(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 September 2006 (28.09.2006)

PCT

(10) International Publication Number
WO 2006/101456 A1

(51) International Patent Classification:
C07D 403/06 (2006.01) *C07D 209/14* (2006.01) *A61P 27/02* (2006.01) *C07D 471/04* (2006.01) *C07D 231/56* (2006.01) *A61P 3/10* (2006.01) *A61K 31/404* (2006.01) *C07D 209/18* (2006.01) *A61P 35/00* (2006.01) *A61P 25/28* (2006.01) *C07D 403/12* (2006.01) *C07D 209/20* (2006.01) *A61K 31/4188* (2006.01)

(21) International Application Number: PCT/SG2006/000065

(22) International Filing Date: 20 March 2006 (20.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/663,213 21 March 2005 (21.03.2005) US
60/663,199 21 March 2005 (21.03.2005) US
60/663,206 21 March 2005 (21.03.2005) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: BICYCLIC HETEROCYCLES HYDROXAMATE COMPOUNDS USEFUL AS HISTONE DEACETYLASE (HDAC) INHIBITORS

(57) Abstract: The present invention relates to hydroxamate compounds which are inhibitors of histone deacetylase. More particularly, the present invention relates to heterocyclic containing compounds and methods for their preparation. These compounds may be useful as medicaments for the treatment of proliferative disorders as well as other diseases involving, relating to or associated with enzymes having histone deacetylase (HDAC) activities.

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BICYCLIC HETEROCYCLES: PREPARATION AND PHARMACEUTICAL APPLICATIONS

FIELD OF THE INVENTION

The present invention relates to hydroxamate compounds that are inhibitors of histone deacetylase (HDAC). More particularly, the present invention relates to bicyclic heterocyclic compounds and methods for their preparation and use. These compounds may be useful as medicaments for the treatment of proliferative disorders as well as other diseases involving, relating to or associated with enzymes having histone deacetylase activities.

BACKGROUND OF THE INVENTION

Local chromatin architecture is generally recognized as an important factor in the regulation of gene expression. The architecture of chromatin, a protein-DNA complex, is strongly influenced by post-translational modifications of the histones which are the protein components. Reversible acetylation of histones is a key component in the regulation of gene expression by altering the accessibility of transcription factors to DNA. In general, increased levels of histone acetylation are associated with increased transcriptional activity, whereas decreased levels of acetylation are associated with repression of gene expression (Wade P.A. et al. Hum. Mol. Genet., **2001**, 10:693-698., De Ruijter A.J.M. et al, Biochem. J., **2003**, 370:737-749). In normal cells, histone deacetylases (HDACs) and histone acetyltransferase together control the level of acetylation of histones to maintain a balance. Inhibition of HDACs results in the accumulation of acetylated histones, which results in a variety of cell type dependent cellular responses, such as apoptosis, necrosis, differentiation, cell survival, inhibition of proliferation and cytostasis.

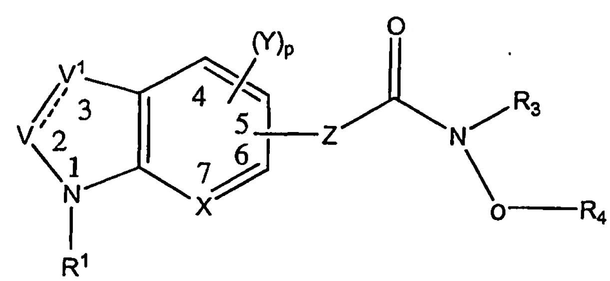
Inhibitors of HDAC have been studied for their therapeutic effects on cancer cells. For example, suberoylanilide hydroxamic acid (SAHA) is a potent inducer of differentiation and/or apoptosis in murine erythroleukemia, bladder, and myeloma cell lines (Richon V.M. et al, Proc. Natl. Acad. Sci. USA, **1996**, 93: 5705-5708, Richon V.M. et al, Proc. Natl. Acad. Sci. USA, **1998**, 95: 3003-3007). SAHA has been shown to suppress the growth of prostate cancer cells *in vitro* and *in vivo* (Butler L.M. et al, Cancer Res. **2000**, 60:5165-5170). Other inhibitors of HDAC that have been widely studied for their anti-cancer activities are trichostatin A (TSA) and trapoxin B (Yoshida M. et al, J. Biol. Chem., **1990**, 265:17174., Kijima M. et al, J. Biol. Chem., **1993**, 268:22429). Trichostatin A is a reversible inhibitor of mammalian HDAC. Trapoxin B is a cyclic

tetrapeptide, which is an irreversible inhibitor of mammalian HDAC. However, due to the in vivo instability of these compounds they are less desirable as anti-cancer drugs. Recently, other small molecule HDAC inhibitors have become available for clinical evaluation (US6,552,065). Additional HDAC inhibiting compounds have been reported in the literature (Bouchain G. et al, J. Med. Chem., **2003**, 46:820-830) and patents (WO 03/066579A2, WO 01/38322 A1). The in vivo activity of such inhibitors can be directly monitored by their ability to increase the amount of acetylated histones in the biological sample. HDAC inhibitors have been reported to interfere with neurodegenerative processes, for instance, HDAC inhibitors arrest polyglutamine-dependent neurodegeneration (Nature, **2001**, 413(6857): 739-43). In addition, HDAC inhibitors have also been known to inhibit production of cytokines such as TNF, IFN, IL-1 which are known to be implicated in inflammatory diseases and/or immune system disorders. (J. Biol. Chem. **1990**; 265(18): 10230-10237; Science, **1998**; 281: 1001-1005; Dinarello C.A. and Moldawer L.L.: Proinflammatory and anti-inflammatory cytokines in rheumatoid arthritis. A primer for clinicians. 2nd Edition, Amergen Inc., **2000**).

Nevertheless, there is still a need to provide further HDAC inhibitors that would be expected to have useful, improved pharmaceutical properties in the treatment of diseases such as cancer, neurodegenerative diseases, disorders involving angiogenesis and inflammatory and/or immune system disorders.

SUMMARY OF THE INVENTION

In one aspect the present invention provides a compound of the formula (I):



Formula (I)

wherein

the bond between V and V^1 is a single or a double bond;

(a) when the bond between V and V^1 is a double bond then

V is CR^2 or N;

V^1 is CR^{2a} or N;

wherein V and V^1 are not both N, and further wherein if V^1 is N then X is N;

(b) when the bond between V and V^1 is a single bond then

V is CR^2_2 or NR^2;

V^1 is CR^{2a}_2 or NR^2;

X is N or CY;

R^1 is selected from the group consisting of: H, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, arylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynyloxy, cycloalkylkoxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, arylalkyloxy, phenoxy, benzyloxy, amino, alkylamino, aminoalkyl, acylamino, arylamino, sulfonylamino, sulfinylamino, COOH, COR^6, $COOR^6$, $-CONHR^6$, $-NHCOR^6$, $-NHCOOR^6$, $-NHCONHR^6$, $C(=NOH)R^6$, -alkylNCOR^6, alkoxycarbonyl, alkylaminocarbonyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, aminosulfonyl, SR^7 and acyl, each of which may optionally be substituted,

or R^1 = L,

or R^1 is a group of the formula:

$$-(CR^{20}R^{21})_m-(CR^{22}R^{23})_n-(CR^{24}R^{25})_o-NR^{26}R^{27};$$

wherein each R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} is independently selected from the group consisting of: H, halogen, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, arylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkoxyheteroaryl, alkenyloxy, alkynyloxy, cycloalkylkoxy, heterocycloalkyloxy, aryloxy, arylalkyloxy, phenoxy, benzyloxy heteroaryloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, alkoxycarbonyl,

alkylaminocarbonyl, sulfonyl, alkylsulfonyl, aminosulfonyl, arylsulfonyl, arylsulfinyl -COOH, -C(O)OR^5, -COR^5, -SH, -SR^6, -OR^6 and acyl, each of which may be optionally substituted, or

R^{20} and R^{21} when taken together may form a group of formula =O or =S, and/or

R^{22} and R^{23} when taken together may form a group of formula =O or =S, and/or

R^{24} and R^{25} when taken together may form a group of formula =O or =S;

each R^{26} and R^{27} is independently selected from the group consisting of: H, halogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, arylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynyloxy, cycloalkylkoxy, heterocycloalkyloxy, aryloxy, arylalkyloxy, heteroaryloxy, amino, alkylamino, aminoalkyl, acylamino, arylamino, phenoxy, benzyloxy, COOH, alkoxycarbonyl, alkylaminocarbonyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, aminosulfonyl, SR^5 and acyl, each of which may be optionally substituted,

or R^{26} and R^{27}, together with the nitrogen atom to which they are attached form an optionally substituted heterocycloalkyl group;

m, n and o are integers independently selected from the group consisting of 0, 1, 2, 3 and 4;

R^2 is selected from the group consisting of: H, halogen, -CN, -NO_2, -CF_3, -OCF_3, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, arylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynyloxy, cycloalkylkoxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, arylalkyloxy, phenoxy, benzyloxy, amino, alkylamino, aminoalkyl, acylamino, arylamino, sulfonylamino, sulfinylamino, -COOH, -COR^6, -COOR^6, -CONHR^6, -NHCOR^6, -NHCOOR^6, -NHCONHR^6, C(=NOH)R^6, -alkylNCOR^6, alkoxycarbonyl, alkylaminocarbonyl, sulfonyl, alkylsulfonyl, alkylsulfinyl,

arylsulfonyl, arylsulfinyl, aminosulfonyl, SR^7 and acyl, each of which may optionally be substituted,
or R^2 = L;

R^{2a} is selected from the group consisting of: H, halogen, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, arylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynyloxy, cycloalkylkoxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, arylalkyloxy, phenoxy, benzyloxy, amino, alkylamino, aminoalkyl, acylamino, arylamino, sulfonylamino, sulfinylamino, -COOH, $-COR^6$, $-COOR^6$, $-CONHR^6$, $-NHCOR^6$, $-NHCOOR^6$, $-NHCONHR^6$, $C(=NOH)R^6$, $-alkylNCOR^6$, alkoxycarbonyl, alkylaminocarbonyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, aminosulfonyl, SR^7 and acyl, each of which may optionally be substituted,
or R^{2a} = L;

or R^2 and R^{2a} are joined such that when taken together with the two carbons to which they are attached they form a cyclic moiety;

each Y is independently selected from the group consisting of: H, halogen, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkoxyheteroaryl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenyloxy, heterocycloalkyloxy, heterocycloalkenyloxy, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, aminoalkyl, alkoxyalky, -COOH $-C(O)OR^6$, $-COR^6$, -SH, $-SR^7$, $-OR^7$, acyl and $-NR^7R^8$, each of which may be optionally substituted;

p is an integer selected from 0, 1 or 2,

R^3 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl each of which may be optionally substituted;

R^4 is selected from the group consisting of: H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl each of which may be optionally substituted;

Each R^5 is independently selected from the group consisting of: H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl each of which may be optionally substituted;

Each R^6 is independently selected from the group consisting of: H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl each of which may be optionally substituted;

Each R^7 and R^8 is independently selected from the group consisting of: H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylheteroalkyl, heteroarylheteroalkyl, and acyl each of which may be optionally substituted;

L is selected from the group consisting of:

a) $L=Cy-L^1-W-$

wherein

Cy is C_1-C_{15} alkyl, aminoalkyl, heteroalkyl heterocycloalkyl, cycloalkyl, aryl, aryloxy or heteroaryl, each of which may be optionally substituted;

L^1 is selected from the group consisting of C_1-C_5 alkyl or C_2-C_5 alkenyl each of which may be optionally substituted;

W is selected from the group consisting of a bond, -O-, -S-, -S(O)-, $-S(O)_2-$, $-N(R^9)-$, $-C(O)N(R^9)-$, $-SO_2N(R^9)-$, $-N(R^9)C(O)-$, $-N(R^9)SO_2-$, and $-N(R^9)-C(O)-N(R^{10})-$;

b) $L=Cy-L^1-W-L^2$

wherein,

Cy is C_1-C_{15} alkyl, aminoalkyl, heterocycloalkyl, cycloalkyl, aryl, aryloxy or heteroaryl, each of which may be optionally substituted;

L^1 and L^2 are the same or different and are independently C_1-C_5 alkyl or C_2-C_5 alkenyl each of which may be optionally substituted;

W is selected from the group consisting of a bond, -O-, -S-, -S(O)-, $-S(O)_2-$, $-N(R^9)-$, $-C(O)N(R^9)-$, $-SO_2N(R^9)-$, $-N(R^9)C(O)-$, $-N(R^9)SO_2-$, and $-N(R^9)-C(O)-N(R^{10})-$;

c) L=Cy-$(CH_2)_k$-W-

wherein,

Cy is C_1-C_{15} alkyl, aminoalkyl, heterocycloalkyl, cycloalkyl, aryl, aryloxy or heteroaryl, each of which may be optionally substituted;

k is 0, 1, 2, 3, 4 or 5;

W is selected from the group consisting of a bond, -O-, -S-, -S(O)-, -$S(O)_2$-, -N(R^9)-, -C(O)N(R^9)-, -SO_2N(R^9)-, -N(R^9)C(O)-, -N(R^9)SO_2-, and –N(R^9)-C(O)-N(R^{10})-;

d) L=L^1-W-L^2

L^1 and L^2 are the same or different and independently selected from C_1-C_5 alkyl or C_2-C_5 alkenyl each of which may be optionally substituted which may be optionally substituted;

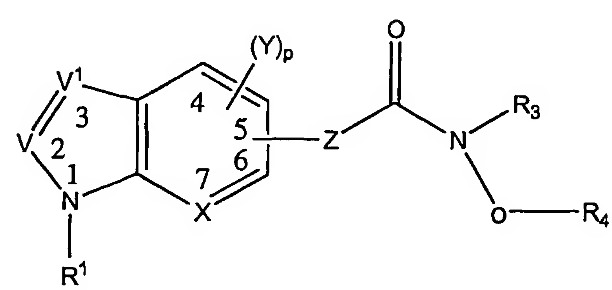
W is selected from the group consisting of a bond, -O-, -S-, -S(O)-, -$S(O)_2$-, -N(R^9)-, -C(O)N(R^9)-, -SO_2N(R^9)-, -N(R^9)C(O)-, -N(R^9)SO_2-, and –N(R^9)-C(O)-N(R^{10})-;

R^9 and R^{10} are the same or different and are independently selected from H, C_1-C_6 alkyl, hydroxyalkyl, heteroalkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl and acyl each of which may be optionally substituted;

Z is a single bond or is selected from the group consisting of -CH_2-, -CH_2CH_2-, -CH=CH- and C_3-C_6 cycloalkyl each of which may be optionally substituted;

or a pharmaceutically acceptable salt or prodrug thereof.

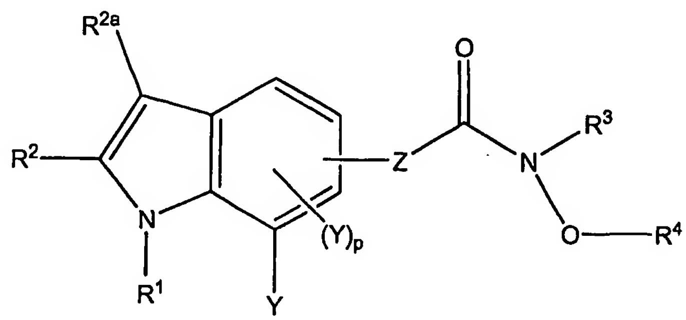
In one embodiment the bond between V and V^1 is a double bond providing compounds of formula (Ia):



Formula (Ia)

Wherein R^1, V, V^1, R^3, R^4, Y, p and X are as defined for compound of formula (I).

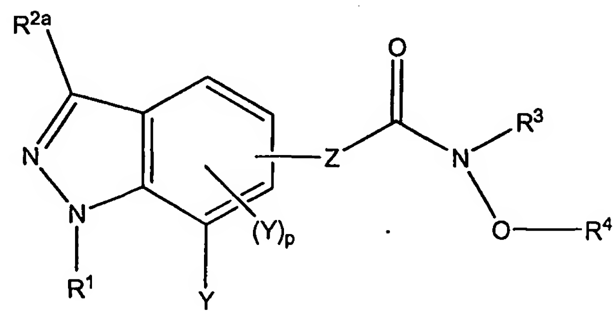
In another embodiment the compound is a compound of formula (Ib):



Formula (Ib)

wherein R^1, R^2, R^{2a}, R^3, R^4, Y, p and Z are as defined for compound of formula (I).

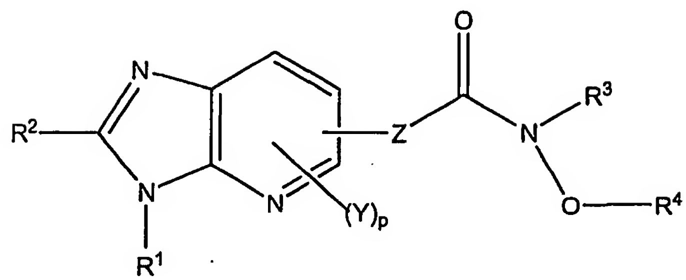
In another embodiment the compound is a compound of formula (Ic):



Formula (Ic)

wherein R^1, R^{2a}, R^3, R^4, Y, p and Z are as defined for compound of formula (I).

In yet an even further preferred embodiment the compound is a compound of formula (Id)



Formula (Id)

wherein R^1, R^{2a}, R^3, R^4, Y, p and Z are as defined for compound of formula (I).

As with any group of structurally related compounds which possess a particular utility, certain groups are preferred for the compounds of Formula (I), (Ia) (Ib), (Ic) and (Id) in their end use application.

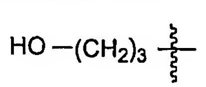
In one embodiment R^1, is selected from the group consisting of H, hydroxyalkyl, alkyl, heteroalkyl, alkoxyalkyl, arylalkyl, heteroarylalkyl, aminoalkyl, heterocycloalkylheteroalkyl, and heterocycloalkyl each of which may be optionally substituted as previously stated.

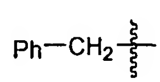
In another embodiment R^1 is selected from the group consisting of H, alkyl, heteroalkyl, alkoxyalkyl, and arylalkyl each of which may be optionally substituted as previously stated.

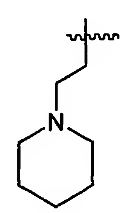
In another embodiment R^1, is selected from the group consisting of hydroxyalkyl, arylalkyl and heterocycloalkylalkyl each of which may be optionally substituted as previously stated.

In another embodiment R^1 is arylalkyl. Specific examples of suitable arylalkyl groups include benzyl and phenethyl.

In one embodiment R^1 is selected from the group consisting of:







In another embodiment when R^1 is alkyl or heteroalkyl then it is not substituted by a cycloalkyl, aryl, heteroaryl, or heterocycloalkyl group.

Specific values of R^1 are: H; methyl; (pyridin-2-yl)methyl; phenylmethyl, (pyridin-3-yl)methyl; (2-pyrollidin-1-yl-ethylamino)-methyl, ethyl; 2-hydroxy-ethyl; 2-(pyridin-2-yl)ethyl; 2-(pyridin-3-yl)ethyl; 2-phenyl-ethyl; 2-carboxy-ethyl; 2-(morpholin-4-yl)-ethyl; 2-(piperidin-1-yl)-ethyl; 2-(pyrollidin-1-yl)-ethyl; 2-dimethylamino-ethyl; 3-dimethylamino-2-methyl-propyl, 2-diethylamino-ethyl; 2-methoxy-ethyl; propyl; 2,3-di-hydroxy-propyl; 3-hydroxy-propyl; 3-methoxy-propyl; 3-isopropoxy-propyl; 2,2-dimethyl-propyl; 3-dimethylamino-propyl; 3-dimethylamino-2,2-dimethyl-propyl; 3-(2-oxo-pyrollidin-1-yl)-propyl; 3-(morpholin-4-yl)-propyl; 3-(imadazol-1-yl)-propyl; 3-(4-methyl-piperidin-1-yl)-propyl; 3-(pyrollidin-1-yl)-propyl; 4-dimethylamino-butyl; 5-hydroxy-pentyl; allyl; benzyl; 3,4,5-trimethoxybenzyl; 2,2-dimethyl propyl; 2,2-dimethyl butyl; 2-methylpropyl; 2-methyl butyl; norbornyl-1-methyl; bicyclo[3.3.0]octane-3-methyl.

In another embodiment R^1 is a group of the formula:

$$-(CR^{20}R^{21})_m-(CR^{22}R^{23})_n-(CR^{24}R^{25})_o-NR^{26}R^{27};$$

wherein R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, m, n and o are as defined in formula (I).

In one form of this embodiment R^1 is a group of the formula:

$-(CR^{20}R^{21})-(CR^{22}R^{23})-NR^{26}R^{27}$;

In a further form of this embodiment R^1 is a group of the formula

$-CH_2-CH_2-NR^{26}R^{27}$

In a further form of this embodiment R^1 is a group of the formula:

$-(CR^{20}R^{21})-(CR^{22}R^{23})-(CR^{24}R^{25})-NR^{26}R^{27}$.

In a further form of this embodiment R^1 is a group of the formula:
$-CH_2-C(CH_3)_2CH_2-NR^{26}R^{27}$

In one form of these embodiments R^{26} and R^{27} are each independently selected from the group consisting of H, or alkyl. If R^{26} and R^{27} are alkyl then in one embodiment they are independently selected from C_1-C_{10} alkyl. In another embodiment they are

independently selected from C_1-C_6 alkyl. Examples of specific values of alkyl are methyl, ethyl, propyl, isopropyl, 2,2-dimethyl-propyl, butyl, isobutyl, tert-butyl, pentyl, 2,4,4-trimethyl-pentyl, and hexyl, each of which may be optionally substituted.

In another embodiment R^{26} and R^{27} together with the nitrogen to which they are attached from an optionally substituted heterocycloalkyl group, which in certain embodiment is a 5 or 6 membered heterocycloalkyl group. Example of heterocycloalkyl groups that may be formed by the combination of R^{26} and R^{27} include pyrrolidine and piperidine.

In one embodiment R^2 is selected from the group consisting of H, alkyl, hydroxyalkyl, alkoxyalkyl, aryl, heteroaryl, heteroalkyl, cycloalkyl, heterocycloalkylalkyl, heterocycloalkyl heteroalkyl, arylalkyl, heteroarylalkyl, aryl heteroalkyl, heteroarylheteroalkyl, and L, each of which may be optionally substituted as previously stated.

In one embodiment R^2 is an arylalkyl moiety. Examples of suitable arylalkyl moieties include benzyl and phenethyl.

In another embodiment R^2 is an alkyl group which in one embodiment is selected from C_1-C_{10} alkyl. In another embodiment R^2 is selected from C_1-C_6 alkyl. Examples of specific values of alkyl are methyl, ethyl, propyl, isopropyl, 2,2-dimethyl-propyl, butyl, isobutyl, tert-butyl, pentyl, 2,4,4-trimethyl-pentyl, and hexyl, each of which may be optionally substituted.

In another embodiment if R^2 is alkyl or heteroalkyl then it is not substituted by a cycloalkyl, aryl, heteroaryl, or heterocycloalkyl group.

Specific values of R^2 include : H; methyl; (pyridin-2-yl)methyl; (pyridin-3-yl)methyl; ethyl; 2-hydroxy-ethyl; 2-(pyridin-2-yl)ethyl; 2-(pyridin-3-yl)ethyl; 2-phenyl-ethyl; 2-carboxy-ethyl; 2-(morpholin-4-yl)-ethyl; 2-(piperidin-1-yl)-ethyl; 2-(pyrollidin-1-yl)-ethyl; 2-dimethylamino-ethyl; 2-diethylamino-ethyl; 2-methoxy-ethyl; propyl; 2,3-di-hydroxy-propyl; 3-hydroxy-propyl; 3-methoxy-propyl; 3-isopropoxy-propyl; 2,2-dimethyl-propyl; 3-dimethylamino-propyl; 3-dimethylamino-2,2-dimethyl-propyl; 3-(2-oxo-pyrollidin-1-yl)-propyl; 3-(morpholin-4-yl)-propyl; 3-(imadazol-1-yl)-propyl; 3-(4-methyl-piperidin-1-yl)-propyl; 3-(pyrollidin-1-yl)-propyl; 4-dimethylamino-butyl; 5-hydroxy-pentyl; allyl; benzyl; 3,4,5-trimethoxybenzyl; 2,2-dimethyl propyl; butyl, 2,2-dimethyl

butyl; 2-methylpropyl; 2-methyl butyl; norbornyl-1-methyl; bicyclo[3.3.0]octane-3-methyl.

In another embodiment R^2 and R^{2a} are joined such that together with the carbon atoms to which they are attached they form a cyclic group containing from 3 to 20 atoms in the cyclic moiety. In one form of this embodiment the R^2 and R^{2a} are joined such that together with the carbon atoms to which they are attached they form a cyclohexenyl group.

In one embodiment R^{2a} is selected from the group consisting of H, alkyl, aryl, heteroaryl, heteroalkyl, cycloalkyl, heterocycloalkylalkyl, heterocycloalkyl heteroalkyl, arylheteroalkyl and L, each of which may be optionally substituted as previously stated.

In one specific embodiment R^{2a} is selected from the group consisting of heterocycloalkylalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl and arylheteroalkyl, each of which may be optionally substituted.

In another embodiment if R^{2a} is alkyl or heteroalkyl then it is not substituted by a cycloalkyl, aryl, heteroaryl, or heterocycloalkyl group.

In another embodiment R^{2a} is an arylheteroalkyl group, a heterocycloalkylheteroalkyl group or a heteroarylheteroalkyl group and has the formula:

$$B\text{-}(CH_2)_r\text{-}NR^9\text{-}(CH_2)_s\text{—}\xi\text{—}$$

wherein B is Aryl, heteroaryl or heterocycloalkyl.

r and s are integers independently selected from 0 to 6;

R^9 is selected from the group consisting of H, C_1-C_6 alkyl, hydroxyalkyl, heteroalkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl and acyl each of which may be optionally substituted.

In one form of this embodiment the group is an arylheteroalkyl group and has the formula:

$$Ar\text{-}(CH_2)_r\text{-}NR^9\text{-}(CH_2)_s\text{—}\xi\text{—}$$

wherein Ar is aryl;

r and s are integers independently selected from 0 to 6;

R^9 is selected from the group consisting of H, C_1-C_6 alkyl, hydroxyalkyl, heteroalkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl and acyl each of which may be optionally substituted.

In a specific form of this embodiment r = 2 and s = 1 and R^{2a} is a group of formula:

$$Ar\text{-}(CH_2)_2\text{-}NR^9\text{-}(CH_2)\text{—}\xi\text{—}$$

In another specific embodiment R^{2a} is a heterocycloalkylheteroalkyl group and has the formula:

$$Het\text{-}(CH_2)_r\text{-}NR^9\text{-}(CH_2)_s\text{—}\xi\text{—}$$

wherein Het is heterocycloalkyl;

r and s are integers independently selected from 0 to 6;

R^9 is selected from the group consisting of H, C_1-C_6 alkyl, hydroxyalkyl, heteroalkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl and acyl each of which may be optionally substituted.

In one form of this embodiment r = 2 and s = 1 and R^{2a} is a group of formula:

$$Het\text{-}(CH_2)_2\text{-}NR^9\text{-}(CH_2)\text{—}\xi\text{—}$$

In another specific embodiment R^{2a} is:

Cy-L_1-W-

wherein

Cy is C_1-C_{15} alkyl, aminoalkyl, heteroalkyl heterocycloalkyl, cycloalkyl, aryl, aryloxy or heteroaryl, each of which may be optionally substituted;

L^1 is selected from the group consisting of C_1-C_5 alkyl or C_2-C_5 alkenyl each of which may be optionally substituted;

W is selected from the group consisting of a bond, -O-, -S-, -S(O)-, -S(O)$_2$-, -N(R^9)-, -C(O)N(R^9)-, -SO$_2$N(R^9)-, -N(R^9)C(O)-, -N(R^9)SO$_2$-, and –N(R^9)-C(O)-N(R^{10})-;

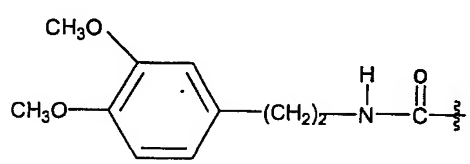
In one form of this embodiment R^{2a} is a group of formulae:

Cy-L^1-N(R^9)C(O)- wherein

Cy is C_1-C_{15} alkyl, aminoalkyl, heterocycloalkyl, cycloalkyl, aryl, aryloxy or heteroaryl, each of which may be optionally substituted;.

L^1 is selected from the group consisting of C_1-C_5 alkyl, which may be optionally substituted.

In one embodiment R^{2a} is a group of formula:



Further specific values of R^{2a} are: H; methyl; benzylamino-methyl; dibenzylamino-methyl; (3-phenylpropyl-amino)-methyl, pyrrolidin-1-yl-methyl; [2-(4-fluoro-phenyl)-acetylamino]-methyl; 2-methyl-pyrollidin-1-yl-methyl, [2-(4-methoxy-phenyl)-acetylamino]-methyl; (2-pyrollidin-1-yl-ethylamino)-methyl; (phenethylamino)methyl; 4-methoxy-benzylamino-methyl; (2-hydroxyethyl)-phenethyl-amino)-methyl; benzyloxy-methyl; phenylacetylamino-methyl; 1-amino-2-phenyl-ethyl; 2-benzylamino-ethyl; 2-(3-methoxy-phenyl)-ethyl; 2-(pyridin-3-yl)ethyl; 2-(2-phenoxyacetylamino)-ethyl; 2-benzenesulphonylamino-ethyl; 2-phenyl-ethyl; isopropyl; 2-phenyl-propyl; 3-phenyl-propyl; 3-phenoxy-propyl; 3-(1H-indol-3-yl)-propyl; 4-methoxy-phenyl; 4-fluoro-phenyl; 4-benzyloxy-3-methoxy-phenyl; isobutyl; cyclohexyl; octyl; benzyl; pyridin-2-yl; pyridin-4-yl; thiophen-3-yl; benzylsulfanyl, and 2-phenylmethansulfanyl.

If R^1 or R^2 or R^{2a} are substituted, particularly preferred substituents are selected from the group consisting of: halogen, =O, =S, -CN, $-NO_2$, alkyl, alkenyl, heteroalkyl, haloalkyl, alkynyl, aryl, cycloalkyl, heterocycloalkyl, heteroaryl, hydroxy, hydroxyalkyl, alkoxy, alkylamino, aminoalkyl, acylamino, phenoxy, alkoxyalkyl, benzyloxy, alkylsulfonyl, arylsulfonyl, aminosulfonyl, $-C(O)OR^6$, COOH, SH, and acyl.

Each Y may be the same or different and is generally selected from the group consisting of H, halogen, C_1-C_4 alkyl, $-CF_3$, $-NO_2$, $-C(O)R^6$, $-OR^7$, $-SR^7$, -CN and $-NR^7R^8$.

If p is 1 the substitution is preferably at the 4 or 7 position of the ring. If p is 2 the substituents are preferably at the 4 and 7 position of the ring. p is preferably 0.

R^3 is preferably H, C_1-C_6 alkyl, or acyl, more preferably H or C_1-C_4 alkyl, most preferably H;
R^4 is preferably H or C_1-C_4 alkyl, most preferably H;
R^5 is preferably H, C_1-C_4 alkyl, heteroalkyl, or acyl, most preferably methyl;
R^6 is preferably H, C_1-C_4 alkyl, heteroalkyl or acyl, most preferably C_1-C_4 alkyl;
R^7 and R^8 are preferably selected from the group consisting of H, C_1-C_6 alkyl, C_4-C_9cycloalkyl, C_4-C_9heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl

In one specific embodiment the Z moiety is selected from the group consisting of $-CH_2-$, $-CH_2-CH_2-$ and $-CH=CH-$. In one specific embodiment the Z moiety is a group of formula $-CH=CH-$. The group of formula $-CH=CH-$ is desirably in the "E" configuration. The Z moiety is generally at the 5 or 6 positions. In one specific embodiment the Z moiety is at the 5 position.

In addition to compounds of the invention as described above the embodiments disclosed are also directed to pharmaceutically acceptable salts, pharmaceutically acceptable prodrugs, and pharmaceutically active metabolites of such compounds, and pharmaceutically acceptable salts of such metabolites. Such compounds, salts, prodrugs and metabolites are at times collectively referred to herein as "HDAC inhibiting agents" or "HDAC inhibitors". In certain embodiments the compounds disclosed are used to modify deacetylase activity, in some cases histone deacetylase activity and in some cases HDAC 8, or HDAC 1 activity.

The embodiments disclosed also relate to pharmaceutical compositions each comprising a therapeutically effective amount of a HDAC inhibiting agent of the embodiments described with a pharmaceutically acceptable carrier or diluent for treating cellular proliferative ailments. The term "effective amount" as used herein indicates an amount necessary to administer to a host to achieve a therapeutic result, e.g., inhibition of proliferation of malignant cancer cells, benign tumor cells or other proliferative cells.

The invention also relates to pharmaceutical compositions including a compound of the invention with a pharmaceutically acceptable carrier, diluent or excipient.

In yet a further aspect the present invention provides a method of treatment of a disorder caused by, associated with or accompanied by disruptions of cell proliferation and/or angiogenesis including administration of a therapeutically effective amount of a compound of formula (I).

In one embodiment the method includes administration of a compound of (Ia) (Ib), (Ic) or (Id) as described herein.

In one embodiment the disorder is selected from the group consisting of but not limited to cancer (e.g. breast cancer, colon cancer, prostate cancer, pancreatic cancer, leukemias, lymphomas, ovarian cancers, neuroblastomas, melanoma, inflammatory diseases/immune system disorders, angiofibroma, cardiovascular diseases (e.g. restenosis, arteriosclerosis), fibrotic diseases (e.g. liver fibrosis), diabetes, autoimmune diseases, chronic and acute neurodegenerative disease like disruptions of nerval tissue, Huntington's disease and infectious diseases like fungal, bacterial and viral infections. In another embodiment the disorder is a proliferative disorder. In one embodiment the proliferative disorder is cancer. The cancer can include solid tumors or hematologic malignancies.

The invention also provides agents for the treatment of a disorder caused by, associated with or accompanied by disruptions of cell proliferation and/or angiogenesis including a compound of formula (I) as disclosed herein. In one embodiment the agent is an anti-cancer agent. In another embodiment, the agent is an anti-angiogenesis agent.

In one embodiment the agent contains a compound of formula (Ia) (Ib), (Ic) or (Id) as described herein.

The invention also relates to the use of compounds of formula (I) in the preparation of a medicament for the treatment of a disorder caused by, associated with or accompanied by disruptions of cell proliferation and/or angiogenesis. In one embodiment the disorder is a proliferative disorder. In a specific embodiment the disorder is a cancer.

The compounds of the present invention surprisingly show low toxicity, together with a potent anti-proliferative activity.

In yet a further embodiment the invention provides a method of treatment of a disorder, disease or condition that can be treated by the inhibition of histone deacetylase including administration of a therapeutically effective amount of a compound of formula (I).

In one embodiment the method includes administration of a compound of formula (Ia) (Ib), (Ic) or (Id) as described herein.

In one embodiment the disorder is selected from the group consisting of but not limited to Proliferative disorders (e.g. cancer); Neurodegenerative diseases including Huntington's Disease, Polyglutamine diseases, Parkinson's Disease, Alzheimer's Disease, Seizures, Striatonigral degeneration, Progressive supranuclear palsy, Torsion dystonia, Spasmodic torticollis and dyskinesis, Familial tremor, Gilles de la Tourette syndrome, Diffuse Lewy body disease, Pick's disease, Intracerebral haemorrhage Primary lateral sclerosis, Spinal muscular atrophy, Amyotrophic lateral sclerosis, Hypertrophic interstitial polyneuropathy, Retinitis pigmentosa, Hereditary optic atrophy, Hereditary spastic paraplegia, Progressive ataxia and Shy-Drager syndrome; Metabolic diseases including Type 2 diabetes; Degenerative Diseases of the Eye including Glaucoma, Age-related macular degeneration, macular myopic degeneration, Rubeotic glaucoma, Interstitial keratitis, Diabetic retinopathy, Peter's anomaly retinal degeneration, Cellophane Retinopathy; Cogan's Dystrophy; Corneal Dystrophy; Iris Neovascularization (Rubeosis); Neovascularization of the Cornea; Retinopathy of Prematurity; Macular Edema; Macular Hole; Macular Pucker; Marginal Blepharitis, Myopia, nonmalignant growth of the conjunctiva; Inflammatory diseases and/or Immune system disorders including Rheumatoid Arthritis (RA), Osteoarthritis, Juvenile chronic arthritis, Graft versus Host disease, Psoriasis, Asthma, Spondyloarthropathy,

Crohn's Disease, inflammatory bowel disease, Colitis Ulcerosa, Alcoholic hepatitis, Diabetes, Sjoegrens's syndrome, Multiple Sclerosis, Ankylosing spondylitis, Membranous glomerulopathy, Discogenic pain, Systemic Lupus Erythematosus, allergic contact dermatitis; Disease involving angiogenesis including cancer, psoriasis, rheumatoid arthritis; Psychological disorders including bipolar disease, schizophrenia, depression and dementia; Cardiovascular Diseases including Heart failure, restenosis, cardiac hypertrophy and arteriosclerosis; Fibrotic diseases including liver fibrosis, lung fibrosis, cystic fibrosis and angiofibroma; Infectious diseases including Fungal infections, such as *Candida Albicans*, Bacterial infections, Viral infections, such as Herpes Simplex, Protozoal infections, such as Malaria, Leishmania infection, Trypanosoma brucei infection, Toxoplasmosis and coccidiosis, and Haematopoietic disorders including thalassemia, anemia and sickle cell anemia.

The invention also provides agents for the treatment of a disorder, disease or condition that can be treated by the inhibition of histone deacetylase including a compound of formula (I) as disclosed herein. In one embodiment the agent is an anti-cancer agent.

The invention also relates to the use of compounds of formula (I) in the preparation of a medicament for the treatment of a disorder, disease or condition that can be treated by the inhibition of histone deacetylase.

The invention also provides a method for inhibiting cell proliferation including administration of an effective amount of a compound according to formula (I).

In yet an even further aspect the invention provides a method of treatment of a neurodegenerative disorder in a patient including administration of a therapeutically effective amount of a compound of formula (I). In one embodiment the method includes administration of a formula (Ia) (Ib), (Ic) or (Id) as described herein. In one specific embodiment the neurodegenerative disorder is Huntington's Disease.

The invention also provides agents for the treatment of neurodegenerative disorder including a compound of formula (I) as disclosed herein. In one embodiment the agent is an anti-Huntington's disease agent.

The invention also relates to the use of compounds of formula (I) in the preparation of a medicament for the treatment of a neurodegenerative disorder. In a specific embodiment the neurodegenerative disorder is Huntington's Disease.

In yet an even further aspect the invention provides a method of treatment of an inflammatory disease and/or immune system disorder in a patient including administration of a therapeutically effective amount of a compound of formula (I). In one embodiment the method includes administration of a compound of formula (Ia), (Ib), (Ic) or (Id) as described herein. In one embodiment the inflammatory disease and/or immune system disorder is rheumatoid arthritis. In another embodiment the inflammatory disease and/or immune system disorder is Systemic Lupus Erythematosus.

The invention also provides agents for the treatment of inflammatory disease and/or immune system disorder including a compound of formula (I) as disclosed herein.

The invention also relates to the use of compounds of formula (I) in the preparation of a medicament for the treatment of inflammatory disease and/or immune system disorder. In one embodiment the inflammatory disease and/or immune system disorder is rheumatoid arthritis. In another embodiment the inflammatory disease and/or immune system disorder is Systemic Lupus Erythematosus.

In yet an even further aspect the invention provides a method of treatment of eye disease mediated by HDAC inhibition in a patient including administration of a therapeutically effective amount of a compound of formula (I). In one embodiment the method includes administration of a compound of formula (Ia), (Ib), (Ic) or (Id) as described herein. In one embodiment, the eye disease is macular degeneration. In another embodiment, the eye disease is glaucoma. In another embodiment, the eye disease is retinal degeneration.

The invention also provides agents for the treatment of eye disease mediated by HDAC inhibition including a compound of formula (I). In one embodiment, the eye disease is macular degeneration. In another embodiment, the eye disease is glaucoma. In another embodiment, the eye disease is retinal degeneration.

The invention also relates to the use of compounds of formula (I) in the preparation of a medicament for the treatment of eye disease mediated by HDAC inhibition. The method preferably includes administration of a compound of formula (Ia), (Ib), (Ic) or (Id) as described herein. In one embodiment, the eye disease is macular

degeneration. In another embodiment, the eye disease is glaucoma. In another embodiment, the eye disease is retinal degeneration.

DETAILED DESCRIPTION OF THE INVENTION

There are disclosed hydroxamate compounds, for example heterocycles containing hydroxamic acid in one of the substituents that may be inhibitors of deacetylases, including but not limited to inhibitors of histone deacetylases. The hydroxamate compounds may be suitable for prevention or treatment of a disorder caused by, associated with or accompanied by disruptions of cell proliferation and/or angiogenesis when used either alone or together with a pharmaceutically acceptable carrier, diluent or excipient. An example of such a disorder is cancer.

As used herein the term 'cancer' is a general term intended to encompass the vast number of conditions that are characterised by uncontrolled abnormal growth of cells.

It is anticipated that the compounds of the invention will be useful in treating various cancers including but not limited to bone cancers including Ewing's sarcoma, osteosarcoma, chondrosarcoma and the like, brain and CNS tumours including acoustic neuroma, neuroblastomas, glioma and other brain tumours, spinal cord tumours, breast cancers, colorectal cancers, advanced colorectal adenocarcinomas, colon cancers, endocrine cancers including adenocortical carcinoma, pancreatic cancer, pituitary cancer, thyroid cancer, parathyroid cancer, thymus cancer, multiple endocrine neoplasma, gastrointestinal cancers including stomach cancer, esophageal cancer, small intestine cancer, Liver cancer, extra hepatic bile duct cancer, gastrointestinal carcinoid tumour, gall bladder cancer, genitourinary cancers including testicular cancer, penile cancer, prostate cancer, gynaecological cancers including cervical cancer, ovarian cancer, vaginal cancer, uterus/endometrium cancer, vulva cancer, gestational trophoblastic cancer, fallopian tube cancer, uterine sarcoma, head and neck cancers including oral cavity cancer, lip cancer, salivary gland cancer, larynx cancer, hypopharynx cancer, orthopharynx cancer, nasal cancer, paranasal cancer, nasopharynx cancer, leukemias including childhood leukemia, acute lymphocytic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, hairy cell leukemia, acute promyelocytic leukemia, plasma cell leukemia, myelomas, haematological disorders including myelodysplastic syndromes, myeloproliferative disorders, aplastic anemia, Fanconi anemia, Waldenstroms Macroglobulinemia, lung cancers including small cell lung cancer, non-small cell lung cancer, lymphomas including Hodgkin's disease, non-Hodgkin's lymphoma, cutaneous

T-cell lymphoma, peripheral T-cell lymphoma, AIDS related Lymphoma, B-cell lymphoma, Burkitt's lymphoma; eye cancers including retinoblastoma, intraocular melanoma, skin cancers including melanoma, non-melanoma skin cancer, merkel cell cancer, soft tissue sarcomas such as childhood soft tissue sarcoma, adult soft tissue sarcoma, Kaposi's sarcoma, urinary system cancers including kidney cancer, Wilms tumour, bladder cancer, urethral cancer, and transitional cell cancer.

Examples of cancers that may be treated by the compounds of the present invention are breast cancer, lung cancer, ovarian cancer, prostate cancer, head and neck cancer, renal cancer (e.g. renal cell carcinoma), gastric cancer, colon cancer, colon cancer, colorectal cancer and brain cancer.

Examples of cancers that may be treated by compounds of the present invention include but are not limited to B-cell lymphoma (e.g. Burkitt's lymphoma), leukemias (e.g. Acute promyelocytic leukemia), cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma.

Examples of cancers that may be treated by compounds of the present invention include solid tumors and hematologic malignancies.

The compounds may also be used in the treatment of a disorder involving, relating to or, associated with dysregulation of histone deacetylase (HDAC).

There are a number of disorders that have been implicated by or known to be mediated at least in part by HDAC activity, where HDAC activity is known to play a role in triggering disease onset, or whose symptoms are known or have been shown to be alleviated by HDAC inhibitors. Disorders of this type that would be expected to be amenable to treatment with the compounds of the invention include the following but not limited to: Proliferative disorders (e.g. cancer); Neurodegenerative diseases including Huntington's Disease, Polyglutamine diseases, Parkinson's Disease, Alzheimer's Disease, Seizures, Striatonigral degeneration, Progressive supranuclear palsy, Torsion dystonia, Spasmodic torticollis and dyskinesis, Familial tremor, Gilles de la Tourette syndrome, Diffuse Lewy body disease, Pick's disease, Intracerebral haemorrhage Primary lateral sclerosis, Spinal muscular atrophy, Amyotrophic lateral sclerosis, Hypertrophic interstitial polyneuropathy, Retinitis pigmentosa, Hereditary optic atrophy, Hereditary spastic paraplegia, Progressive ataxia and Shy-Drager syndrome; Metabolic diseases including Type 2 diabetes; Degenerative Diseases of

the Eye including Glaucoma, Age-related macular degeneration, macular myopic degeneration, Rubeotic glaucoma, Interstitial keratitis, Diabetic retinopathy, Peter's anomaly retinal degeneration, Cellophane Retinopathy; Cogan's Dystrophy; Corneal Dystrophy; Iris Neovascularization (Rubeosis); Neovascularization of the Cornea; Retinopathy of Prematurity; Macular Edema; Macular Hole; Macular Pucker; Marginal Blepharitis, Myopia, nonmalignant growth of the conjunctiva; Inflammatory diseases and/or Immune system disorders including Rheumatoid Arthritis (RA), Osteoarthritis, Juvenile chronic arthritis, Graft versus Host disease, Psoriasis, Asthma, Spondyloarthropathy, Crohn's Disease, inflammatory bowel disease, Colitis Ulcerosa, Alcoholic hepatitis, Diabetes, Sjoegrens's syndrome, Multiple Sclerosis, Ankylosing spondylitis, Membranous glomerulopathy, Discogenic pain, Systemic Lupus Erythematosus, allergic contact dermatitis; Disease involving angiogenesis including cancer, psoriasis, rheumatoid arthritis; Psychological disorders including bipolar disease, schizophrenia, depression and dementia; Cardiovascular Diseases including Heart failure, restenosis, cardiac hypertrophy and arteriosclerosis; Fibrotic diseases including liver fibrosis, lung fibrosis, cystic fibrosis and angiofibroma; Infectious diseases including Fungal infections, such as *Candida Albicans*, Bacterial infections, Viral infections, such as Herpes Simplex, Protozoal infections, such as Malaria, Leishmania infection, Trypanosoma brucei infection, Toxoplasmosis and coccidiosis, and Haematopoietic disorders including thalassemia, anemia and sickle cell anemia.

As used herein, the term unsubstituted means that there is no substituent or that the only substituents are hydrogen.

The term "optionally substituted" as used throughout the specification denotes that the group may or may not be further substituted or fused (so as to form a condensed polycyclic system), with one or more non-hydrogen substituent groups. Preferably the substituent groups are one or more groups independently selected from the group consisting of halogen, =O, =S, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, heteroarylalkyl, arylalkyl, cycloalkylalkenyl, heterocycloalkylalkenyl, arylalkenyl, heteroarylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, arylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxycycloalkyl, alkoxyheterocycloalkyl, alkoxyaryl, alkoxyheteroaryl, alkoxycarbonyl, alkylaminocarbonyl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenyloxy, heterocycloalkyloxy, heterocycloalkenyloxy, aryloxy,

phenoxy, benzyloxy, heteroaryloxy, arylalkyloxy, arylalkyl, heteroarylalkyl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonylamino, sulfinylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, sulfinyl, alkylsulfinyl, arylsulfinyl, aminosulfinylaminoalkyl, -COOH, $-COR^5$, $-C(O)OR^5$, $CONHR^5$, $NHCOR^5$, $NHCOOR^5$, $NHCONHR^5$, $C(=NOH)R^5$, -SH, $-SR^5$, $-OR^5$ and acyl. Substituent groups themselves may be further optionally substituted.

"Halogen" represents chlorine, fluorine, bromine or iodine.

"Alkyl" as a group or part of a group refers to a straight or branched aliphatic hydrocarbon group, preferably a C_1–C_{14} alkyl, more preferably C_1-C_{10} alkyl, most preferably C_1-C_6 unless otherwise noted. Examples of suitable straight and branched C_1-C_6 alkyl substituents include methyl, ethyl, n-propyl, 2-propyl, n-butyl, sec-butyl, t-butyl, hexyl, and the like.

"Alkylamino" includes both monoalkylamino and dialkylamino, unless specified. "Monoalkylamino" means a –NH-Alkyl group, in which alkyl is as defined above. "Dialkylamino" means a $-N(alkyl)_2$ group, in which each alkyl may be the same or different and are each as defined herein for alkyl. The alkyl group is preferably a C_1-C_6 alkyl group.

"Arylamino" includes both mono-arylamino and di-arylamino unless specified. Mono-arylamino means a group of formula aryl NH- in which aryl is as defined herein, di-arylamino means a group of formula $(aryl_2)$ N- where each aryl may be the same or different and each are as defined herein for aryl.

"Acyl" means an alkyl-CO- group in which the alkyl group is as described herein. Examples of acyl include acetyl and benzoyl. The alkyl group is preferably a C_1-C_6 alkyl group.

"Alkenyl" as group or part of a group denotes an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched preferably having 2-14 carbon atoms, more preferably 2-12 carbon atoms, most preferably 2-6 carbon atoms, in the chain. The group may contain a plurality of double bonds in the normal chain and the orientation about each is independently E or Z. Exemplary alkenyl group include, but are not limited to, ethenyl and propenyl.

"Alkoxy" refers to an –O-alkyl group in which alkyl is defined herein. Preferably the alkoxy is a C_1-C_6alkoxy. Examples include, but are not limited to, methoxy and ethoxy.

"Alkenyloxy" refers to an -O- alkenyl group in which alkenyl is as defined herein. Preferred alkenyloxy groups are C_1-C_6 alkenyloxy groups.

"Alkynyloxy" refers to an –O-alkynyl group in which alkynyl is as defined herein. Preferred alkynyloxy groups are C_1-C_6 alkynyloxy groups.

"Alkoxycarbonyl" refers to an –C(O)-O-alkyl group in which alkyl is as defined herein. The alkyl group is preferably a C_1-C_6 alkyl group. Examples include, but not limited to, methoxycarbonyl and ethoxycarbonyl.

"Akylsulfinyl" means a –S(O)-alkyl group in which alkyl is as defined above. The alkyl group is preferably a C_1-C_6 alkyl group. Exemplary alkylsulfinyl groups include, but not limited to, methylsulfinyl and ethylsulfinyl.

"Alkylsulfonyl" refers to a –S(O)$_2$-alkyl group in which alkyl is as defined above. The alkyl group is preferably a C_1-C_6 alkyl group. Examples include, but not limited to methylsulfonyl and ethylsulfonyl.

"Alkynyl as a group or part of a group means an aliphatic hydrocarbon group containing a carbon-carbon triple bond and which may be straight or branched preferably having from 2-14 carbon atoms, more preferably 2-12 carbon atoms in the chain, preferably 2-6 carbon atoms in the chain. Exemplary structures include, but are not limited to, ethynyl and propynyl.

"Alkylaminocarbonyl" refers to an alkylamino-C(O)- group in which alkylamino is as defined above.

"Cycloalkyl" refers to a saturated or partially saturated, monocyclic or fused or spiro polycyclic, carbocycle preferably containing from 3 to 9 carbons per ring, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like, unless otherwise specified. It includes monocyclic system such as cyclohexyl, bicyclic systems such as decalin, and polycyclic systems such as adamantane.

"Cycloalkylalkyl" means a cycloalkyl-alkyl- group in which the cycloalkyl and alkyl moieties are as previously described. Exemplary monocycloalkylalkyl groups include cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl.

"Heterocycloalkyl" refers to a saturated or partially saturated monocyclic, bicyclic or polycyclic ring containing at least a heteroatom selected from nitrogen, sulfur, oxygen, preferably from 1 to 3 heteroatoms in at least one ring. Each ring is preferably from 3 to 10 membered, more preferably 4 to 7 membered. Examples of suitable heterocycloalkyl substituents include pyrrolidyl, tetrahydrofuryl, tetrahydrothiofuranyl, piperidyl, piperazyl, tetrahydropyranyl, morphilino, 1,3-diazapane, 1,4-diazapane, 1,4-oxazepane, and 1,4-oxathiapane.

"Heterocycloalkenyl" refers to a heterocycloalkyl as described above but containing at least one double bond.

"Heterocycloalkylalkyl" refers to a heterocycloalkyl-alkyl group in which the heterocycloalkyl and alkyl moieties are as previously described. Exemplary heterocycloalkylalkyl groups include (2-tetrahydrofuryl)methyl, (2-tetrahydrothiofuranyl)methyl.

"Heteroalkyl" refers to a straight- or branched-chain alkyl group preferably having from 2 to 14 carbon atoms, more preferably 2 to 10 atoms in the normal chain, one or more of which has been replaced by a heteroatom selected from S, O, and N. Exemplary heteroalkyls include alkyl ethers, secondary and tertiary alkyl amines, alkyl sulfides, and the like.

"Aryl" as a group or part of a group denotes (i) an optionally substituted monocyclic, or fused polycyclic, aromatic carbocycle (ring structure having ring atoms that are all carbon) preferably having from 5 to 12 atoms per ring. Examples of aryl groups include phenyl, naphthyl, and the like; (ii) an optionally substituted partially saturated bicyclic aromatic carbocyclic moiety in which a phenyl and a C_{5-7} cycloalkyl or C_{5-7} cycloalkenyl group are fused together to form a cyclic structure, such as tetrahydronaphthyl, indenyl or indanyl.

"Arylalkenyl" means an aryl-alkenyl- group in which the aryl and alkenyl are as previously described. Exemplary arylalkenyl groups include phenylallyl.

"Arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl moieties are as previously described. Preferred arylalkyl groups contain a C_{1-5} alkyl moiety. Exemplary arylalkyl groups include benzyl, phenethyl and naphthelenemethyl.

"Cycloalkenyl" means an optionally substituted non-aromatic monocyclic or polycyclic ring system containing at least one carbon-carbon double bond and preferably having from 5-10 carbon atoms per ring. Exemplary monocyclic cycloalkenyl rings include cyclopentenyl, cyclohexenyl or cycloheptenyl.

The term "heteroaryl" either alone or part of another group refers to groups containing an aromatic ring (preferably a 5 or 6 membered aromatic ring) having 1 or more heteroatoms as ring atoms in the aromatic ring with the remainder of the ring atoms being carbon atoms. Suitable heteroatoms include oxygen, sulfur, and nitrogen. Examples of heteroaryl include thiophene, benzothiophene, benzofuran, benzimidazole, benzoxazole, benzothiazole, benzisothiazole, naphtho[2,3-b]thiophene, furan, isoindolizine, xantholene, phenoxatine, pyrrole, imidazole, pyrazole, pyridine, pyrazine, pyrimidine, pyridazine, indole, isoindole, 1H-indazole, purine, 4H-quinolidine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, carbazole, phenanthridine, acridine, phenazine, thiazole, isothiazole, phenothiazine, oxazole, isoxazole, furazane, phenoxazine, 2-, 3-, or 4-pyridyl, 2-, 3-, 4-, 5-, or 8-quinolyl, 1-, 3-, 4-, or 5-isoquinolyl, 1-, 2-, or 3-indolyl, 2-benzothiazolyl, 2-benzo[b]thienyl, benzo[b]furanyl, 2- or 3-thienyl, or the like. More preferred examples include 2- or 3-thienyl, 2-, 3-, or 4-pyridyl, 2- or 3-quinolyl, 1-isoquinolyl, 1- or 2-indolyl, 2-benzothiazolyl, and the like.

"Heteroarylalkyl" means a heteroaryl-alkyl group in which the heteroaryl and alkyl moieties are as previously described. Preferred heteroarylalkyl groups contain a C_1 to C_6 alkyl moiety. Exemplary heteroarylalkyl groups include pyridylmethyl.

"Lower alkyl" as a group means unless otherwise specified, an aliphatic hydrocarbon group which may be straight or branched having 1 to 6 carbon atoms in the chain, more preferably 1 to 4 carbons such as methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl).

In Formula (I), as well as in Formulae (Ia)-(Id) defining sub-sets of compounds within Formula (I), there is shown a heterocyclic ring system. Within this ring system, there are substitutable positions at the 4-, 5-, 6-, and/or 7-ring positions. In each of Formulae

(I), (Ia), (Ib), (Ic), (Id) there is a requirement for attachment of an acidic moiety at one of the ring positions. This acidic moiety may be provided by but is not limited to groups containing, a hydroxamic acid or salt derivatives of such acid which when hydrolysed would provide the acidic moiety. In some embodiments the acidic moiety may be attached to the ring position through an alkylene group such as $-CH_2-$ or $-CH_2CH_2-$, or an alkenyl group such as -CH=CH-. In one embodiment the positions for attachment of the acidic moiety are the 5– and 6–ring positions.

It is understood that included in the family of compounds of Formula (I) are isomeric forms including diastereoisomers, enantiomers, tautomers, and geometrical isomers in "E" or "Z" configurational isomer or a mixture of E and Z isomers. It is also understood that some isomeric forms such as diastereomers, enantiomers, and geometrical isomers can be separated by physical and/or chemical methods and by those skilled in the art.

Some of the compounds of the disclosed embodiments may exist as single stereoisomers, racemates, and/or mixtures of enantiomers and /or diastereomers. All such single stereoisomers, racemates and mixtures thereof are intended to be within the scope of the subject matter described and claimed.

Additionally, Formula (I) is intended to cover, where applicable, solvated as well as unsolvated forms of the compounds. Thus, each formula includes compounds having the indicated structure, including the hydrated as well as the non-hydrated forms.

In addition to compounds of the Formula (I), the HDAC inhibiting agents of the various embodiments include pharmaceutically acceptable salts, prodrugs, and active metabolites of such compounds, and pharmaceutically acceptable salts of such metabolites.

The term "Pharmaceutically acceptable salts" refers to salts that retain the desired biological activity of the above-identified compounds, and include pharmaceutically acceptable acid addition salts and base addition salts. Suitable pharmaceutically acceptable acid addition salts of compounds of Formula I may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, sulfuric, and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, heterocyclic carboxylic and sulfonic classes of organic acids, examples of which are formic, acetic, propionic, succinic, glycolic,

gluconic, lactic, malic, tartaric, citric, fumaric, maleic, alkyl sulfonic, arylsulfonic. Suitable pharmaceutically acceptable base addition salts of compounds of Formula I include metallic salts made from lithium, sodium, potassium, magnesium, calcium, aluminium, and zinc, and organic salts made from organic bases such as choline, diethanolamine, morpholine. Other examples of organic salts are: ammonium salts, quaternary salts such as tetramethylammonium salt; amino acid addition salts such as salts with glycine and arginine. Additional information on pharmaceutically acceptable salts can be found in Remington's Pharmaceutical Sciences, 19th Edition, Mack Publishing Co., Easton, PA 1995. In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds, agents and salts may exist in different crystalline or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulae.

"Prodrug" means a compound which is convertible *in vivo* by metabolic means (e.g. by hydrolysis, reduction or oxidation) to a compound of formula (I). For example an ester prodrug of a compound of formula (I) containing a hydroxyl group may be convertible by hydrolysis *in vivo* to the parent molecule. Suitable esters of compounds of formula (I) containing a hydroxyl group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-β-hydroxynaphthoates, gestisates, isethionates, di-*p*-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, *p*-toluenesulphonates, cyclohexylsulphamates and quinates. As another example an ester prodrug of a compound of formula (I) containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule. (Examples of ester prodrugs are those described by F.J. Leinweber, Drug Metab. Res.,18:379, 1987).

Preferred HDAC inhibiting agents include those having an IC_{50} value of 10 μM or less.

Administration of compounds within Formula (I) to humans can be by any of the accepted modes for enteral administration such as oral or rectal, or by parenteral administration such as subcutaneous, intramuscular, intravenous and intradermal routes. Injection can be bolus or via constant or intermittent infusion. The active compound is typically included in a pharmaceutically acceptable carrier or diluent and in an amount sufficient to deliver to the patient a therapeutically effective dose. In various embodiments the inhibitor compound may be selectively toxic or more toxic to rapidly proliferating cells, e.g. cancerous tumors, than to normal cells.

The term "therapeutically effective amount" or "effective amount" is an amount sufficient to effect beneficial or desired results. An effective amount can be administered in one or more administrations. An effective amount is typically sufficient to palliate, ameliorate, stabilize, reverse, slow or delay the progression of the disease state. A therapeutically effective amount can be readily determined by a skilled practitioner by the use of conventional techniques and by observing results obtained in analogous circumstances. In determining the effective amount a number of factors are considered including the species of the patient, its size, age, general health, the specific disease involved, the degree or severity of the disease, the response of the individual patient, the particular compound administered, the mode of administration, the bioavailability of the compound, the dose regimen selected, the use of other medication and other relevant circumstances.

In using the compounds of the invention they can be administered in any form or mode which makes the compound bioavailable. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular characteristics of the compound selected, the condition to be treated, the stage of the condition to be treated and other relevant circumstances. We refer the reader to Remingtons Pharmaceutical Sciences, 19th edition, Mack Publishing Co. (1995) for further information.

The compounds of the present invention can be administered alone or in the form of a pharmaceutical composition in combination with a pharmaceutically acceptable carrier, diluent or excipient. The compounds of the invention, while effective themselves, are typically formulated and administered in the form of their pharmaceutically acceptable salts as these forms are typically more stable, more easily crystallised and have increased solubility.

The compounds are, however, typically used in the form of pharmaceutical compositions which are formulated depending on the desired mode of administration. As such in a further embodiment the present invention provides a pharmaceutical composition including a compound of Formula (I) and a pharmaceutically acceptable carrier, diluent or excipient. The compositions are prepared in manners well known in the art.

The invention in other embodiments provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical

compositions of the invention. In such a pack or kit can be found a container having a unit dosage of the agent(s). The kits can include a composition comprising an effective agent either as concentrates (including lyophilized compositions), which can be diluted further prior to use or they can be provided at the concentration of use, where the vials may include one or more dosages. Conveniently, in the kits, single dosages can be provided in sterile vials so that the physician can employ the vials directly, where the vials will have the desired amount and concentration of agent(s). Associated with such container(s) can be various written materials such as instructions for use, or a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The compounds of the invention may be used or administered in combination with one or more additional drug (s) that include chemotherapeutic drugs or HDAC inhibitor drugs and/or procedures (e.g. surgery, radiotherapy) for the treatment of the disorder/diseases mentioned. The components can be administered in the same formulation or in separate formulations. If administered in separate formulations the compounds of the invention may be administered sequentially or simultaneously with the other drug (s).

In addition to being able to be administered in combination with one or more additional drugs that include chemotherapeutic drugs or HDAC inhibitor drugs the compounds of the invention may be used in a combination therapy. When this is done the compounds are typically administered in combination with each other. Thus one or more of the compounds of the invention may be administered either simultaneously (as a combined preparation) or sequentially in order to achieve a desired effect. This is especially desirable where the therapeutic profile of each compound is different such that the combined effect of the two drugs provides an improved therapeutic result

Pharmaceutical compositions of this invention for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating

materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminium monostearate and gelatin.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

Solid dosage forms for oral administration include capsules, dragees, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes.

If desired, and for more effective distribution, the compounds can be incorporated into slow release or targeted delivery systems such as polymer matrices, liposomes, and microspheres.

The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax

which are solid at room temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

Dosage forms for topical administration of a compound of this invention include powders, patches, sprays, ointments and inhalants. The active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives, buffers, or propellants which may be required.

A preferred dosage will be a range from about 0.01 to 300 mg per kilogram of body weight per day. A more preferred dosage will be in the range from 0.1 to 100 mg per kilogram of body weight per day, more preferably from 0.2 to 80 mg per kilogram of body weight per day, even more preferably 0.2 to 50 mg per kilogram of body weight per day. A suitable dose can be administered in multiple sub-doses per day.

As discussed above, the compounds of the embodiments disclosed inhibit histone deacetylases. The enzymatic activity of a histone deacetylase can be measured using known methodologies (Yoshida M. et al, J. Biol. Chem., **1990**, 265:17174, J. Taunton et al, Science **1996**, 272: 408). In certain embodiments, the histone deacetylase inhibitor interacts with and/or reduces the activity of more than one known histone deacetylase in the cell, which can either be from the same class of histone deacetylase or different class of histone deacetylase.. In some other embodiments, the histone deacetylase inhibitor interacts and reduces the activity of predominantly one histone deacetylase, for example HDAC-1, HDAC-2, HDAC-3 or HDAC-8 which belongs to Class I HDAC enzymes (De Ruijter A.J.M. et al, Biochem. J., **2003**, 370:737-749). HDACs can also target non-histone substrates to regulate a variety of biological functions implicated in disease pathogenesis. These non-histone substrates include Hsp90, α-tubulin, p53, NFkb and HIF1a (Drummond et al., Annu. Rev. Pharmacol. Toxicol. **2004**, 45:495). Certain preferred histone deacetylase inhibitors are those that interact with, and/or reduce the activity of a histone deacetylase which is involved in tumorigenesis, and these compounds may be useful for treating proliferative diseases. Examples of such cell proliferative diseases or conditions include cancer (include any metastases), psoriasis, and smooth muscle cell proliferative disorders such as restenosis. The inventive compounds may be particularly useful for treating tumors such as breast cancer, colon cancer, lung cancer, ovarian cancer, prostate cancer, head and/or neck cancer, or renal, gastric, pancreatic cancer and brain cancer as well as hematologic malignancies such as lymphoma and leukemias. In addition, the inventive compounds may be useful for treating a proliferative disease that is refractory

to the treatment with other chemotherapeutics; and for treating hyperproliferative condition such as leukemias, psoriasis and restenosis. In other embodiments, compounds of this invention can be used to treat pre-cancer conditions or hyperplasia including familial adenomatous polyposis, colonic adenomatous polyps, myeloid dysplasia, endometrial dysplasia, endometrial hyperplasia with atypia, cervical dysplasia, vaginal intraepithelial neoplasia, benign prostatic hyperplasia, papillomas of the larynx, actinic and solar keratosis, seborrheic keratosis and keratoacanthoma.

Additionally compounds of the various embodiments disclosed herein may be useful for treating neurodegenerative diseases, and inflammatory diseases and/or immune system disorders.

The disorder may be selected from the group consisting of cancer, inflammatory diseases and/or immune system disorders (e.g. rheumatoid arthritis, systemic lupus erythematosus), angiofibroma, cardiovascular diseases, fibrotic diseases, diabetes, autoimmune diseases, chronic and acute neurodegenerative disease like Huntington's disease, Parkinson's disease, disruptions of nerval tissue and infectious diseases like fungal, bacterial and viral infections. In another embodiment the disorder is a proliferative disorder.

The histone deacetylase inhibitors of the invention have significant antiproliferative effects and promote differentiation, cell cycle arrest in the G1 or G2 phase, and induce apoptosis.

SYNTHESIS OF DEACETYLASE INHIBITORS

The agents of the various embodiments may be prepared using the reaction routes and synthesis schemes as described below, employing the techniques available in the art using starting materials that are readily available. The preparation of particular compounds of the embodiments is described in detail in the following examples, but the artisan will recognize that the chemical reactions described may be readily adapted to prepare a number of other agents of the various embodiments. For example, the synthesis of non-exemplified compounds may be successfully performed by modifications apparent to those skilled in the art, e.g. by appropriately protecting interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. A list of suitable protecting groups in organic synthesis can be found in T.W. Greene and P. G. M. Wuts' Protective Groups in Organic Synthesis, 3rd Edition, Wiley-InterScience, 1999. Alternatively,

other reactions disclosed herein or known in the art will be recognized as having applicability for preparing other compounds of the various embodiments.

Reagents useful for synthesizing compounds may be obtained or prepared according to techniques known in the art.

In the examples described below, unless otherwise indicated, all temperatures in the following description are in degrees Celsius and all parts and percentages are by weight, unless indicated otherwise.

Various starting materials and other reagents were purchased from commercial suppliers, such as Aldrich Chemical Company or Lancaster Synthesis Ltd., and used without further purification, unless otherwise indicated. Tetrahydrofuran (THF) and N,N-dimethylformamide (DMF) were purchased from Aldrich in SureSeal bottles and used as received. All solvents were purified by using standard methods in the art, unless otherwise indicated.

The reactions set forth below were performed under a positive pressure of nitrogen, argon or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks are fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven-dried and/or heat-dried. Analytical thin-layer chromatography was performed on glass-backed silica gel 60 F 254 plates (E Merck (0.25 mm)) and eluted with the appropriate solvent ratios (v/v). The reactions were assayed by TLC and terminated as judged by the consumption of starting material.

The TLC plates were visualized by UV absorption or with a p-anisaldehyde spray reagent or a phosphomolybdic acid reagent (Aldrich Chemical, 20wt% in ethanol) which was activated with heat, or by staining in iodine chamber. Work-ups were typically done by doubling the reaction volume with the reaction solvent or extraction solvent and then washing with the indicated aqueous solutions using 25% by volume of the extraction volume (unless otherwise indicated). Product solutions were dried over anhydrous sodium sulfate prior to filtration, and evaporation of the solvents was under reduced pressure on a rotary evaporator and noted as solvents removed in vacuo. Flash column chromatography (Still et al, J. Org. Chem., **1978**, 43:2923) was conducted using E Merck-grade flash silica gel (47-61 mm) and a silica gel:crude

material ratio of about 20:1 to 50:1, unless otherwise stated. Hydrogenolysis was done at the pressure indicated or at ambient pressure.

^{1}H NMR spectra was recorded on a Bruker instrument operating at 400 MHz, and ^{13}C-NMR spectra was recorded operating at 100 MHz. NMR spectra are obtained as $CDCl_3$ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm and 77.00 ppm) or CD_3OD (3.4 and 4.8 ppm and 49.3 ppm), or an internal tetramethylsilane standard (0.00 ppm) when appropriate. Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened, dd = doublet of doublets, dt = doublet of triplets. Coupling constants, when given, are reported in Hertz.

Mass spectra were obtained using LC/MS either in ESI or APCI. All melting points are uncorrected.

All final products had greater than 90% purity (by HPLC at wavelengths of 220 nm and 254 nm).

The following examples are intended to illustrate the embodiments disclosed and are not to be construed as being limitations thereto. Additional compounds, other than those described below, may be prepared using the following described reaction scheme or appropriate variations or modifications thereof.

SYNTHESIS

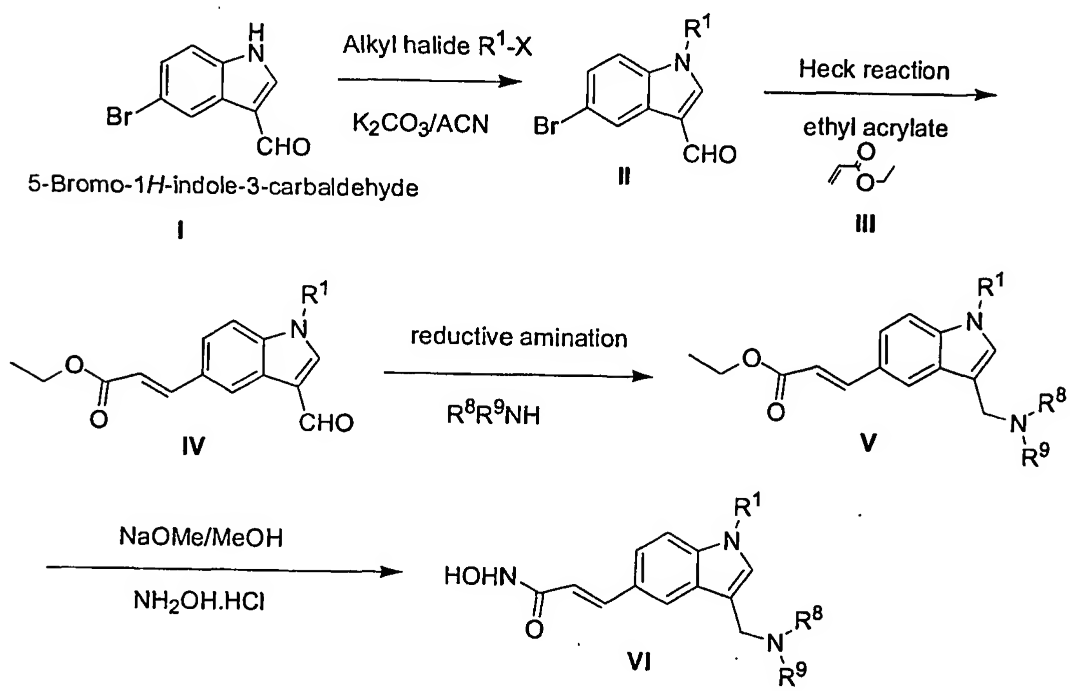
SYNTHESIS OF COMPOUNDS OF FORMULA Ib

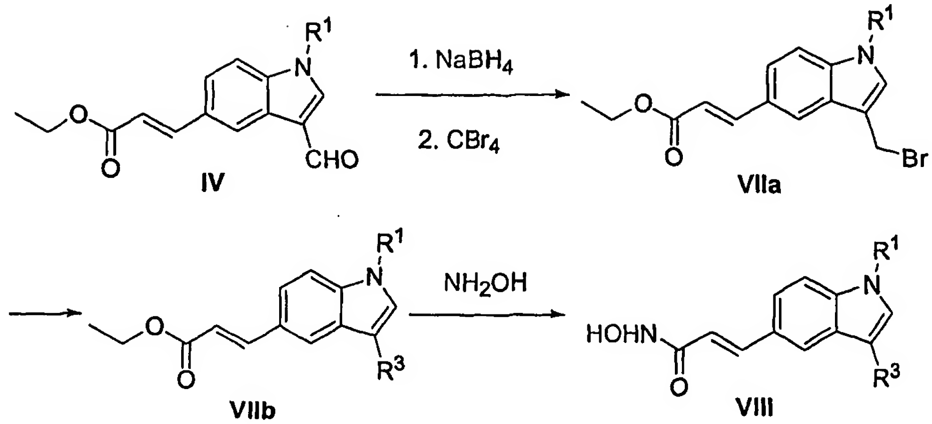
Scheme I illustrates the general procedure used for preparing compounds of formula Ib, wherein R^2, and each Y are hydrogens, and R^1 is either hydrogen or substituted. For example, in the case of Z is –CH=CH- and attached to C_5-position in Formula I, such compound(s) can be synthesized by analogous method illustrated in Scheme I starting with a substituted indole (e.g. *5-Bromo-1H-indole-3-carbaldehyde*), which can be alkylated at the indole nitrogen under basic conditions to give **II**. The N-alkylated indole derivative was then reacted with ethyl acrylate under Heck reaction condition to provide the desired alkenoic ester **IV**. The aldehyde group in **IV** was then reacted with appropriate amine component (R_8R_9NH) to give the reductive amination product. When the reductive amination product is a secondary amine it can be further reacted with an appropriate aldehyde, or an appropriate alkyl halide to produce a tertiary amine. Finally the carboxylic ester group was converted to the hydroxamic acid derivative by reacting with appropriate hydroxylamine or N-alkyl hydroxylamine

(NHR^3OR^4 where R^3 and R^4 are defined as above in Formula I). Specifically, the hydroxamate compounds **VI** were prepared by a known synthesis method (J. Med. Chem., **2002**, *45*:753-757). Examples 1, 2, 3, 10 &11 were synthesized according to Scheme I. Compounds of Formula Ib, for example **Example 4,** in which the indole nitrogen is not alkylated, can be successfully prepared by Scheme **I.** In an alternative method, a Heck reaction can be first performed on 5-Bromo-1H-indole-3-carbaldehyde to give the indole acrylate, which is followed by N-alkylation of indole to give **IV.** Following a reductive amination **IV** is converted to the desired amine which can be converted to the desired hydroxamic acid. Examples 6 - 9 were prepared by this alternative synthetic route.

Additionally, compounds of general structure **VIII** could be prepared from indole aldehyde **IV.** For example, the aldehyde group can be reduced to the primary alcohol under mild reduction conditions, and the resulting alcohol can be subsequently converted to a good leaving group such as a bromide **VIIa** by methods known in the literature. The reactive **VIIa** can be reacted with carbon nucleophiles or oxo anions or thiolates to give 1,3-substituted indoles **VIIb,** and subsequently to the desired hydroxamate **VIII** as depicted in Formula I. Alternatively, 1,3-substituted indoles may be prepared by methodologies in which the 3-substituent is introduced during indole ring formation [Org Lett, **2004**, 6:79-82] and in certain 3-substituents the substituents can be further modified.

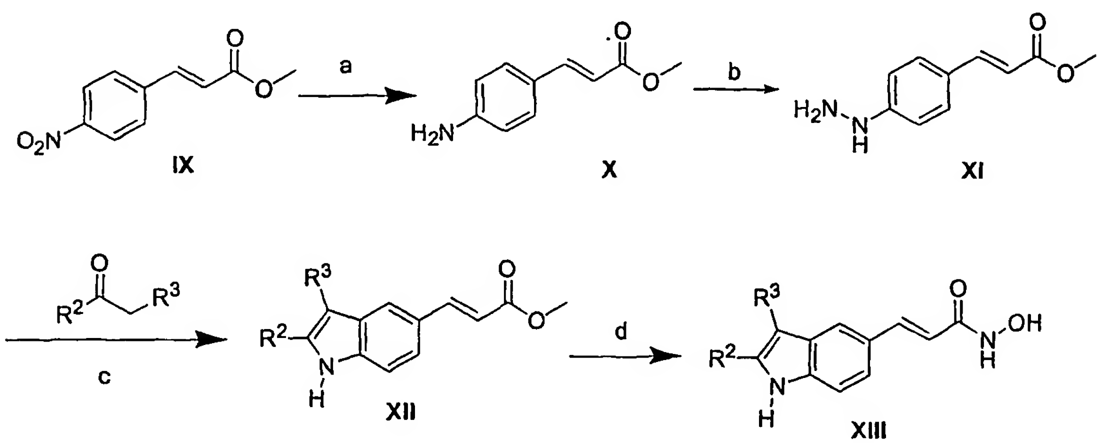
Scheme I





Preparation of 2,3-substituted indole derivatives can be accomplished by reactions known in the literature (Seble Wagaw et al, JACS, **1999**, 121:10251-10262) and is illustrated in Scheme II. For example, in the case of Z is –CH=CH- and attached to C_5-position in Formula I wherein X and Y are hydrogens and R1 is either hydrogen or substituted, such compound(s) can be synthesized by analogous method illustrated in Scheme II starting with a substituted indole (e.g. *4-nitro cinnamic ester* **IX**). Following the reaction sequence as depicted in Scheme II, 2,3-substituted indoles esters **XII** can be obtained. Finally the carboxylic ester group can be converted to the hydroxamic acid in Formula I by established synthesis method (J. Med. Chem., **2002**, 45:753-757).

Scheme II



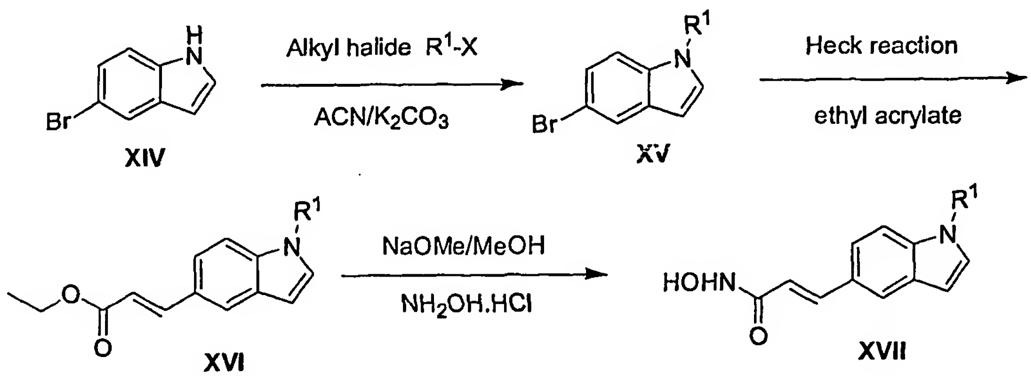
Reagents and conditions: (a) $SnCl_2$ (10 equiv), MeOH, 60 °C. (b) 1. $NaNO_2$, HCl. 2. $SnCl_2$ (10 equiv), MeOH. (c) TsOH, EtOH, reflux. (d) $NH_2OH.HCl$, MeONa, MeOH.

In addition to the method depicted in Scheme II, 2,3-substituted indole derivatives can be prepared by other methodologies which are known in the literature [J. Org. Chem,

1997, 62, 2676; J. Am. Chem. Soc, **1999**, 121:3791-3792]. These 2,3-substituted indoles can be extended to 1,2,3-substituted indoles of Formula I, by alkylation of the indole nitrogen. Examples 16, 18, 19 were prepared according to Scheme II.

The compounds of formula (Ib) may also be produced using the methodology in scheme (III).

Scheme III:

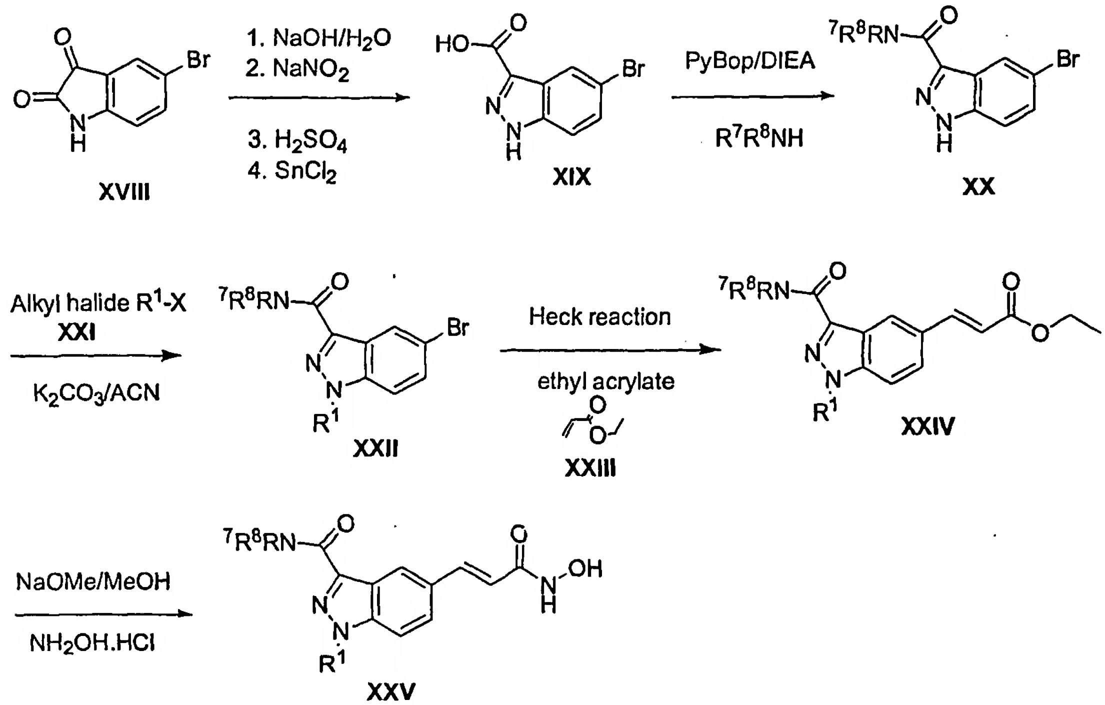


Accordingly reaction of the brominated indole (**XIV**) with an appropriate alkyl halide leads to the alkylated bromo indole (**XV**). This can then be subjected to the Heck reaction to introduce a protected acid moiety at the position-5 (**XVI**) which can then be converted into the hydroxamic acid using standard procedures (**XVII**). An alternative starting material can be 5-bromo indoline.

<u>SYNTHESIS OF COMPOUNDS OF FORMULA Ic</u>

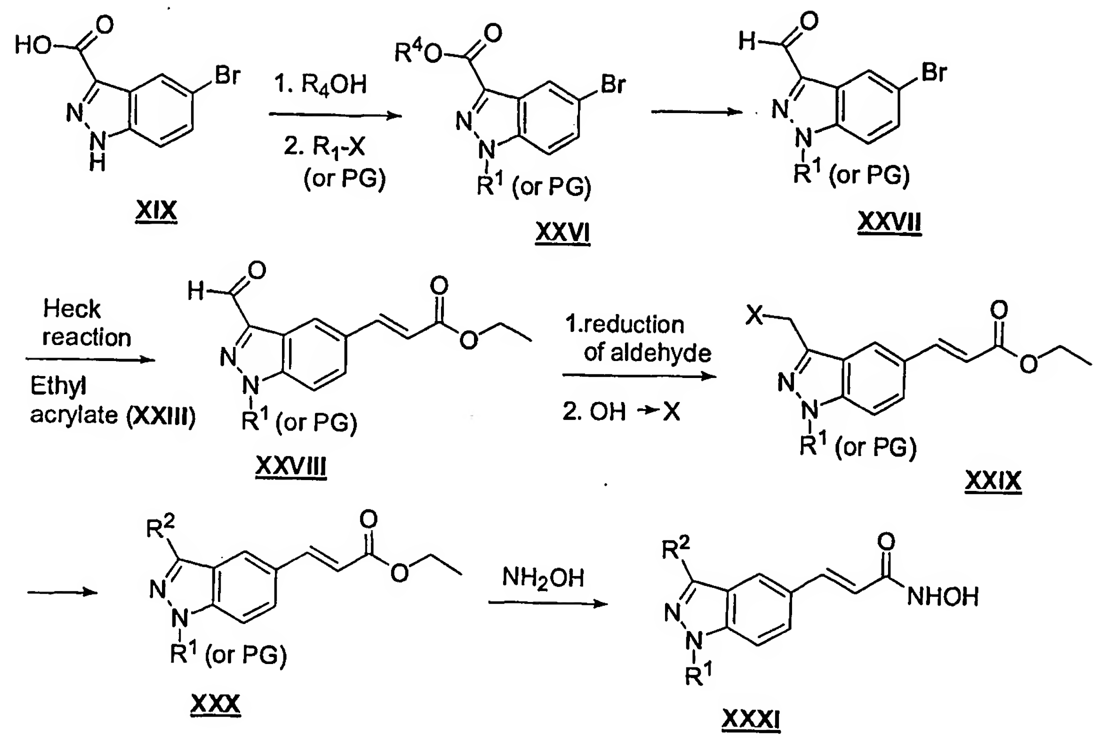
Scheme IV illustrates the general procedure used for preparing compounds of formula Ic. Such compound(s) can be synthesized by analogous method illustrated in Scheme IV starting with 5-bromoisatin (**XVIII**) which can be converted to indazole **XIX** by methods known in the literature. The indazole carboxylate **XIX** was reacted with a primary or secondary amine together with a coupling agent such as PyBop to form the amide **XX**. The indazole nitrogen was then alkylated by reaction with an alkyl halide **XXI**. The N-alkylated indazole derivative **XXII** was then reacted with ethyl acrylate **XXIII** under Heck reaction condition to provide the desired alkenoic ester **XXIV** which was subsequently converted to the hydroxamic acid **XXV** by a known synthesis method (J. Med. Chem., **2002**, *45*:753-757).

Scheme IV



Additionally, the carboxylic acid group in structure **XIX** can be transformed to corresponding aldehydes **XXVII** which can be further modified. For example, the aldehyde group can be reduced to the primary alcohol under mild reduction conditions, and the resulting alcohol can be subsequently converted to a good leaving group such as a bromide **XXIX** by methods known in the literature. The reactive intermediate **XXIX** can be reacted with carbon nucleophiles or oxo anions or thiolates to give 1,3-substituted indazoles **XXX** as illustrated in Scheme V.

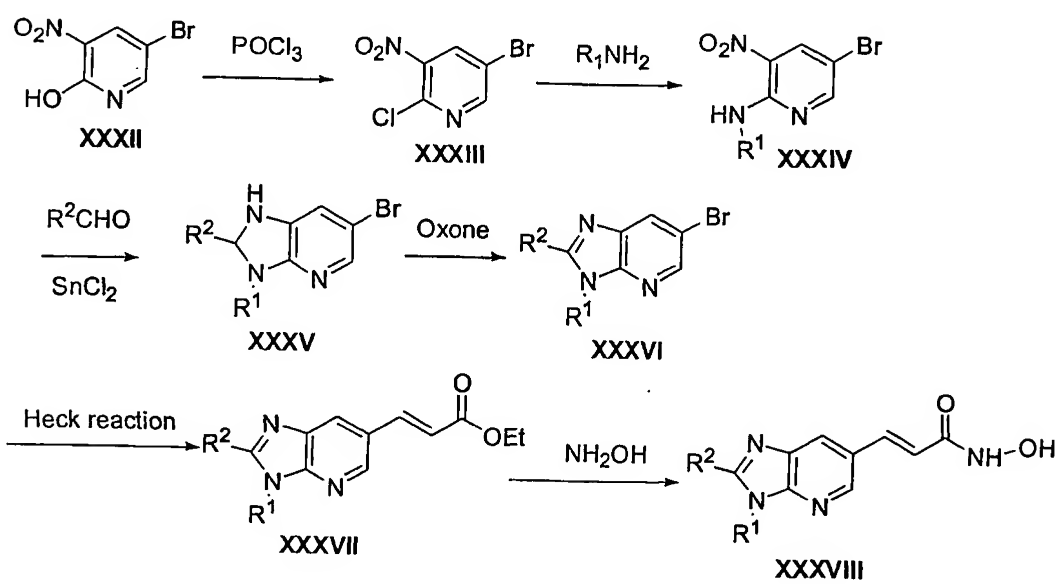
Scheme V



SYNTHESIS OF COMPOUND OF FORMULA Id

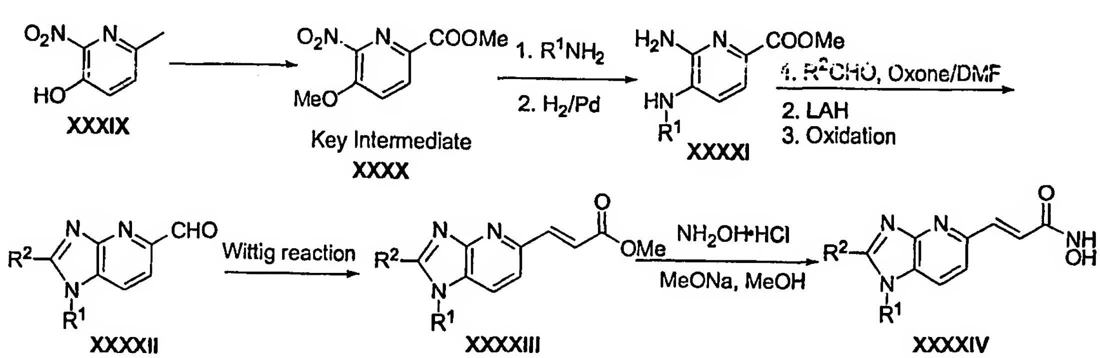
The compounds of formula Id may be synthesized using the procedure outlined in scheme VI

Scheme VI



Specifically, the hydroxamate compounds **XXXVIII** can be synthesized by the synthetic route shown in Scheme VI. The readily available 5-Bromo-3-nitro-pyridin-2-ol **XXXII** was converted to the 2-Cl derivative **XXXIII** by treating with $POCl_3$, and **XXXIII** was then reacted with an amine to give 5-Bromo-3-nitro-pyridin-2-amine **XXXIV** The 2-amino compound was reacted with aldehyde and tin chloride, then followed by oxidation with Oxone to give compound **XXXVI.** Heck reaction of **XXXVI** and ethyl acrylate afforded compound **XXXVII.** The hydroxamate compounds **XXXVIII** were obtained by a known synthesis method (J. Med. Chem., **2002**, *45*, 753-757).

Scheme VII



Alternatively, the hydroxamate compounds of Formula Id wherein the α,β-unsaturated hydroxamic acid is located adjacent to the pyridine nitrogen, can be synthesized by the synthetic route shown in Scheme VII. 5-Methoxy-6-nitro-pyridine-2-carboxylic acid methyl ester **XXXX** which could be prepared from **XXXIX** According to literature procedure (US 6448281 B1), can be treated with a corresponding amine to produce a 6-nitro-5- amine derivative of pyridine which after hydrogenation would give compound **XXXXI** . Imidazole ring formation can be accomplished by treatment of **XXXXI** with corresponding aldehyde in the presence of Oxone to give compound **XXXXII.** The desired α,β-unsaturated ester **XXXXIII** can be introduced into **XXXXII** by performing Wittig or related reaction on **XXXXII**, using appropriate reagents known in the literature to furnish the α,β-unsaturated ester. The hydroxamate compounds (**XXXXIV**) can be obtained by a known synthesis method (J. Med. Chem., **2002**, *45*, 753-757).

The following preparation and examples are given to enable those skilled in the art to more clearly understand and to practice the subject matter hereof. They should not be

considered as limiting the scope of the disclosure, but merely as being illustrative and representative thereof.

Example 1

3-[1-Benzyl-3-(2-methyl-pyrrolidin-1-ylmethyl)-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide (1)

Step 1

1-benzyl-5-bromo-3-carbaldehyde indole

To a pre-stirred solution of 1.12 g (5.0 mmol) of 5-bromo-1*H* indole 3-carbaldehyde, 0.94 g (5.5 mmol) of benzyl bromide in 40 mL of ACN, 3.5 g (25 mmol) of K_2CO_3 were added. The above mixture was stirred at room temperature. LC-MS showed the reaction completed after 5 hours. ACN was removed on a rotary evaporator and the residue was dissolved in 30 mL of DCM and 20 mL of water. The organic layer was collected and washed again with water, brine, and dried over Na_2SO_4. The crude product 1-benzyl-5-bromo-3-carbaldehyde indole (1.3 g, yield 83%) was obtained after removing the solvent DCM. Purity: 95.8% by HPLC ; t_R=(LC/PDA: Xterra 1S column, 4.6 x 20 mm 3.5μ column; 2.0 mL/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 3.50 min; MS(m/z): 314 $[MH]^+$.

Step 2

Heck reaction

To a pre-stirred solution of 160 mg (0.51 mmol) of 1-benzyl-5-bromo-3-carbaldehyde indole, 250 mg (2.5 mmol) of ethylacrylate, 5.6 mg (0.025 mmol, 5%) of palladium acetate, 30.4 mg (0.1 mmol, 20%) of tri(*o*-toluene)phosphate in 5 mL of DMF, 260 uL of DIEA was added. The resulting solution was degassed for 2 hours before it was heated to 108 °C. The mixture was stirred at the above temperature for 20 hours. After cool down, $NaHCO_3$ and ethylacetate (EA) were added to the reaction mixture, the organic layer was collected. The aqueous layer was extracted with EA for 2 times. The EA extracts were combined and washed with water and $NaHCO_3$ and brine and dried over Na_2SO_4. The product 3-(1-Benzyl-3-formyl-1*H*-indol-5-yl)-acrylic acid ethyl ester (105 mg, yield: 62%) was purified by chromatography. Solvent system: EA:Hexane=1:4 to 1:2. Purity: 98.3% by HPLC; t_R=(LC/PDA: Xterra 1S column, 4.6 x 20 mm 3.5μ column; 2.0 mL/min, gradient 5-95% B over 10 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 5.12 min; MS(m/z): 334 $[MH]^+$.

Step 3

Reductive amination

To a pre-stirred solution of 100 mg (0.30 mmol) of 3-(1-Benzyl-3-formyl-1H-indol-5-yl)-acrylic acid ethyl ester, 31 mg (0.36 mmol) of 2-methyl pyrrolidine in 10 mL of dried DCM, was added 18 mg (0.30 mmol) of acetic acid. The resulting solution was stirred at room temperature for 1.5 hours, 95 mg (0.45 mmol) of sodium borohydride triacetate ($NaBH(OAc)_3$) was added. The above mixture was stirred at room temperature over night. The reaction was quenched by adding $NaHCO_3$ and the organic layer was collected. The organic layer was washed with water and brine and dried over Na_2SO_4. The product (67 mg, 55%) was purified by column. Solvent system: EA:Hexane=1:1 to 80% EA plus 1% of TEA. Purity 99% by HPLC; t_R==(LC/PDA: Xterra 1S column, 4.6 x 20 mm 3.5μ column; 2.0 mL/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 2.99 min; MS(m/z): 403 $[MH]^+$.

Step 4

Hydroxamic acid formation

To a pre-stirred solution of 30 mg (0.077 mmol) of precursor ester, 53 mg (0.77 mmol) of hydroxylamine HCl salt in 2 mL of dried MeOH, was added 0.32 mL (4.9M in MeOH, 1.6 mmol) of sodium methoxide. The resulting solution was stirred at room temperature for 16 hours. The reaction was quenched by adding 1M HCl and the product was purified by reversed phase HPLC. 6mg of product was obtained (yield: 20%). Purty: 86.8% by HPLC; t_R==(LC/PDA: Xterra 1S column, 4.6 x 20 mm 3.5μ column; 2.0 mL/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 2.58 min; MS(m/z): 390 $[MH]_+$.

Example 2

3-{1-Benzyl-3-[(2-pyrrolidin-1-yl-ethylamino)-methyl]-1*H*-indol-5-yl}-*N*-hydroxy-acrylamide (2)

The titled compound (**2**) was prepared according to the procedures described in Example 1, by using appropriate starting materials. Yield: 50% based on corresponding ester.

Purity: 99% by HPLC; t_R==(LC/PDA: Xterra 1S column, 4.6 x 20 mm 3.5μ column; 2.0 mL/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 1.64 min; MS(m/z): 419 $[MH]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.79 (4H, m), 2.57 (4H, m), 2.72 (2H, m), 2.89

(2H, m), 4.05 (2H, s), 5.31 (2H, s), 6.44 (1H, m), 7.15 (3H, m), 7.30 (4H, m), 7.33 (1H, m), 7.87 (2H, m), 10.01 (1H, bs), 10.70 (1H, bs).

Example 3

***N*-Hydroxy-3-[1-methyl-3-(phenethylamino-methyl)-1*H*-indol-5-yl]-Acrylamide (3)**

The titled compound (**3**) was prepared according to the procedures described in Example 1, by using appropriate starting materials. 52mg (0.14 mmol) of precursor ester, 90 mg (1.3 mmol) of hydroxylamine HCl salt were dissolved in 3 mL of dried MeOH and followed by adding 0.59 mL (4.9 M in MeOH, 2.9 mmol) of sodium methoxide. The resulting solution was stirred at room temperature for 16 hours. The reaction was quenched by adding 1M HCl and purified by reversed phase HPLC. 18mg of product was obtained. Yield: 35% based on corresponding ester. Purity 99.8% by_HPLC; t_R=(LC/PDA: Xterra 1S column, 4.6 x 20 mm 3.5μ column; 2.0 mL/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 1.86 min; MS(m/z): 350 $[MH]^+$.^1H NMR (400 MHz, DMSO-d_6) δ 2.95 (2H, m), 3.18 (2H, m), 3.83 (3H, s), 4.37 (2H, s), 6.44 (1H, m), 7.26 (3H, m), 7.35 (2H, m), 7.45-7.65 (4H, m), 7.99 (1H, s), 8.84 (1H, s), 10.71 (1H, bs).

Example 4

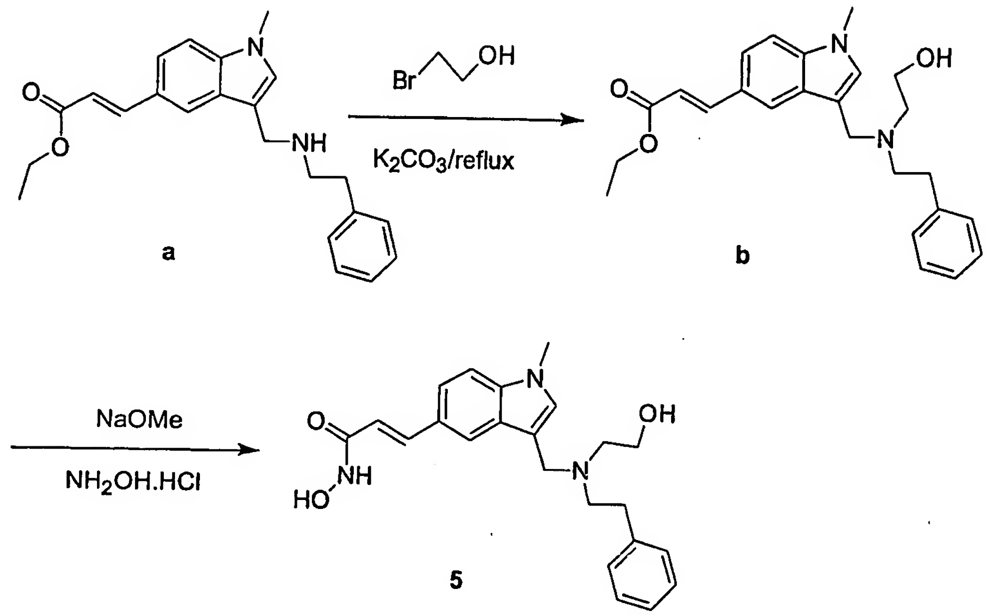
***N*-Hydroxy-3-[3-(phenethylamino-methyl)-1*H*-indol-5-yl]-acrylamide (4)**

The titled compound (**4**) was prepared according to the procedures described in Example 1, by using appropriate starting materials (free indole NH). Yield: 20% based on corresponding ester. Purity: 97.3% by HPLC; t_R=(LC/PDA: Xterra 1S column, 4.6 x 20 mm 3.5μ column; 2.0 mL/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 1.65 min; MS(m/z): 336 $[MH]_+$. ^1H NMR (400 MHz, DMSO-d_6) δ 2.94 (2H, m), 3.20 (2H, m), 4.35 (2H, s), 6.42 (1H, m), 7.26 (3H, m), 7.35 (2H, m), 7.45-7.60 (4H, m), 7.98 (1H, s), 8.80 (1H, s), 10.70 (1H, bs), 11.45 (1H, s).

Example 5

***N*-Hydroxy-3-(3-{[(2-hydroxy-ethyl)-phenethyl-amino]-methyl}-1-methyl-1*H*-indol-5-yl)-acrylamide (5)**

The compound **5** was prepared according to the procedures described in the following. Intermediate **a** was alkylated with bromoethanol under basic condition to provide compound **b**, which was then transformed to corresponding hydroxamate according to procedure described previously to give **5**.



Yield of titled compound **5**: 21% based on corresponding ester. Purity 98.9% by HPLC. HPLC; t_R=(LC/PDA: Xterra 1S column, 4.6 x 20 mm 3.5μ column; 2.0 mL/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 1.84 min; MS(m/z): 394 $[MH]^+$.

Example 6

3-[1-(2-Dimethylamino-ethyl)-3-(phenethylamino-methyl)-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide **(6)**

The titled compound (**6**) was prepared according to the procedures described in Example

1, by using appropriate starting materials Yield: 57% based on corresponding ester. Purity 99.5% by HPLC; t_R=(LC/PDA: Xterra 1S column, 4.6 x 20 mm 3.5μ column; 2.0 mL/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 1.29 min; MS(m/z): 407 $[MH]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.84 (6H, s), 2.96 (2H, m), 3.19 (2H, t), 3.48(2H, m), 4.38 (2H, s), 4.62 (2H, t), 6.48 (1H, m), 7.26 (3H, m), 7.35 (2H, m), 7.51 (1H, m), 7.62 (3H, m), 8.02 (1H, s), 8.93 (1H, s), 10.20 (1H, bs), 10.73 (1H, s).

Example 7

N-Hydroxy-3-[1-(2-methoxy-ethyl)-3-(phenethylamino-methyl)-1*H*-indol-5-yl]-acrylamide (7)

The titled compound (**7**) was prepared according to the procedures described in Example **1**, by using appropriate starting materials. Yield: 40% based on

corresponding ester. Purity 97.1% by HPLC; t_R=(LC/PDA: Xterra 1S column, 4.6 x 20 mm 3.5μ column; 2.0 mL/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 1.87 min; MS(m/z): 394 $[MH]^+$.^{1}H NMR (400 MHz, DMSO-d_6) δ 2.96 (2H, m), 3.20 (3H, s), 3.19 (2H, t), 3.65(4H, m), 4.38 (4H, m), 6.45 (1H, m), 7.26 (3H, m), 7.34 (2H, m), 7.45 (1H, m), 7.58 (3H, m), 7.97 (1H, s), 8.86 (1H, s), 10.71 (1H, bs).

Example 8

3-{1-(2-Dimethylamino-ethyl)-3-[(3-phenyl-propylamino)-methyl]-1*H*-indol-5-yl}-*N*-hydroxy-acrylamide (8)

The titled compound (**8**) was prepared according to the procedures described in Example

1, by using appropriate starting materials

Purity 99% by HPLC; t_R==(LC/PDA: Xterra 1S column, 4.6 x 20 mm 3.5μ column; 2.0 mL/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 1.421 min; MS(m/z): 421 $[MH]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.94 (2H, m), 2.66 (2H, m), 2.84 (6H, s), 2.95 (2H, m), 3.03 (2H, m), 4.38 (2H, s), 4.62 (2H, t), 6.48 (1H, m), 7.21 (3H, m), 7.35 (2H, m), 7.52 (1H, m), 7.66 (3H, m), 8.00 (1H, s), 8.80 (1H, s), 10.27 (1H, bs), 10.73 (1H, s).

Example 9

3-[3-(Benzylamino-methyl)-1-(2-methoxy-ethyl)-1*H*-indol-5-yl]-*N*-hydroxy-Acrylamide (9)

The titled compound (**9**) was prepared according to the procedures described in Example

1, by using appropriate starting materials.

Yield: 50% from corresponding ester. Purity 99% by HPLC; t_R=(LC/PDA: Xterra 1S column, 4.6 x 20mm 3.5μ column; 2.0 mL/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 1.742 min; MS(m/z): 380 $[MH]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.22 (3H, s), 3.65 (2H, t), 4.20 (2H, m), 4.38 (4H, m), 6.44 (1H, m), 7.42 (5H, m), 7.51 (2H, m), 7.57 (3H, m), 7.90 (1H, s), 9.20 (1H, s), 10.72 (1H, bs).

Examples 10

***N*-Hydroxy-3-(1-phenethyl-3-pyrrolidin-1-ylmethyl-1*H*-indol-5-yl)-acrylamide (10)**

The titled compound was prepared using the procedure outlined for example 9. Thus alkylation of indole nitrogen with appropriate alkyl halides, followed by Heck reaction, then by reductive amination with appropriate amines, and finally by converting the ester group to the desired hydroxamate.

To a stirred solution of 20 mg (0.051 mmol) of precursor ester, 34 mg (5.1 mmol) of hydroxylamine HCl salt in 1.5 mL of dried MeOH was added 0.3 mL (4.9M in MeOH, 1.0 mmol) of sodium methoxide. The resulting solution was stirred at room temperature for 16 hours. The reaction was quenched by adding 1M HCl and product was purified by reversed phase HPLC. 8 mg of product was obtained. Yield: 40%. Purity:

99 % by HPLC; t_R==(LC/PDA: Xterra 1S column, 4.6 x 20mm 3.5μ column; 2.0 ml/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 2.07min; MS(m/z): 390 $[MH]^+$.

^1H NMR (400 MHz, DMSO-d_6,) δ 1.84-1.91 (4H, m), 3.06 (4H, m), 3.26 (2H, s), 4.48 (4H, m), 6.58 (1H, m), 7.13-7.25 (5H, m), 7.58 (2H, m), 7.60 (2H, m), 8.00 (1H, s), 8.80 (1H, s), 9.58 (1H, bs), 10.68 (1H, s)

Example 11

***N*-Hydroxy-3-{1-phenethyl-3-[(2-pyrrolidin-1-yl-ethylamino)-methyl]-1*H*-indol-5-yl}-acrylamide (11)**

The titled compound was prepared using the procedure outlined for Example 9. Thus alkylation of indole nitrogen with appropriate alkyl halides, followed by Heck reaction, then by reductive amination with appropriate amines, and finally by converting the ester group to the desired hydroxamate.

To a stirred solution of 50 mg (0.051 mmol) of precursor ester, and 70 mg (5.1 mmol) of hydroxylamine HCl salt in 1.5 mL of dried MeOH was added 0.6 mL (4.9M in MeOH, 1.0 mmol) of sodium methoxide. The resulting solution was stirred at room temperature for 16 hours. The reaction was quenched by adding 1M HCl and product was purified by reversed phase HPLC. 30mg of product was obtained (yield: 60%). Purity: 98.5% by HPLC; t_R==(LC/PDA: Xterra 1S column, 4.6 x 20mm 3.5μ column; 2.0 ml/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid;Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 1.83 min; MS(m/z): 433$[MH]^+$.

Example 12

<u>*N*-Hydroxy-3-[1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indol-5-yl]-acrylamide (12)</u>

<u>Step 1</u>

Preparation of 5-Bromo-1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indole

To a pre-stirred of solution of 0.98g (0.005 mol)of 5-bromo indole, 1.87g (0.01 mol) of 1-(2-chloroethyl)pyrrolidine in 30 mLof ACN, 6.9g of K_2CO_3 were added, the above mixture was stirred at room temperature overnight. ACN was removed on rotary evaporator and the residue was dissolved in 30 mL of DCM and 20 mL of water. The organic layer was collected and washed with water again and then with brine and dried over Na_2SO_4. The product 5-Bromo-1-(2-pyrrolidin-1-yl-ethyl)-1H-indole (1.14g, 78%) was purified by column, solvent system: EA:Hexane=1:1 to EA + TEA2%. MS(m/z): 294[MH]$^+$.

<u>Step 2</u>

Preparation of 3-[1-(2-Pyrrolidin-1-yl-ethyl)-1*H*-indol-5-yl]-acrylic acid ethyl ester

To a pre-stirred of 1.1g (3.75mmol) of above alkylation product, 1.87g (18.7 mmol) of ethylacrylate, 171mg (0.19 mmol) of Pd(dpa)$_3$, 228mg (0.75 mmol) of tri(o-toluene)phosphate in 30 mL of DMF, 1.9 mL of DIEA were added. The resulting solution was degassed for 2 hours before it was heated to 108°C. The mixture was stirred at the above temperature for 20 hours. After cool down, the solution was added to aq.$NaHCO_3$ and extracted with ethylacetate (EA).The organic layer was collected. The aqueous layer was extracted with EA twice more and the combined EA extracts was washed with water, $NaHCO_3$, and brine, and dried over Na_2SO_4. The product 3-[1-(2-Pyrrolidin-1-yl-ethyl)-1*H*-indol-5-yl]-acrylic acid ethyl ester (1.22g) was purified by column chromatography. Solvent system: EA:Hexane=1:1 to EA + 2%TEA. MS(m/z): 313 [MH]$^+$.

<u>Step 3:</u>

***N*-Hydroxy-3-[1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indol-5-yl]-acrylamide**

To a pre-stirred solution of 312mg (1.0 mmol) of precursor ester, 690mg (10 mmol) of hydroxylamine HCl salt 10mL of dried MeOH, was added 4.0 mL of sodium methoxide (4.9M in methanol). The resulting solution was stirred at room temperature for 16 hours. The reaction was quenched by adding 1M HCl and purified by reversed phase HPLC. 95mg of product was obtained (yield 30%). Purity: 98.9% by HPLC; t_R==(LC/PDA: Xterra 1S column, 4.6 x 20mm 3.5μ column; 2.0 ml/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 0.998min/10min; MS(m/z): 300 [MH]$^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.88-1.94 (4H, m), 3.02 (4H, m), 3.61 (2H, t), 4.58 (2H, t), 6.47 (1H,

m), 6.59 (1H, s), 7.42-7.47 (2H, m), 7.54-7.60 (2H, m), 7.71 (1H, s), 10.51 (1H, bs), 10.74 (1H, s).

Example 13

3-[1-(2-Dimethylamino-ethyl)-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide(13)

To a pre-stirred solution of 460mg (1.6mmol) of precursor ester, 1.1g (16mmol) of hydroxylamine HCl salt in 10 mL of dried MeOH, was added 6.5 mL of sodium methoxide (4.9M in methanol). The resulting solution was stirred at room temperature for 16 hours. The reaction was quenched by adding 1M HCl and purified by reversed phase HPLC. 90mg of product was obtained (yield 19%). Purity: 98.9% by HPLC; t_R==(LC/PDA: Xterra 1S column, 4.6 x 20mm 3.5µ column; 2.0 ml/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 0.752min; MS(m/z): 274 $[MH]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 2.83 (6H, s), 3.52 (2H, t), 4.59 (2H, t), 6.43 (1H, m), 6.56 (1H, s), 7.42-7.47 (2H, m), 7.54-7.60 (2H, m), 7.77 (1H, s), 10.16 (1H, s).

Example 14

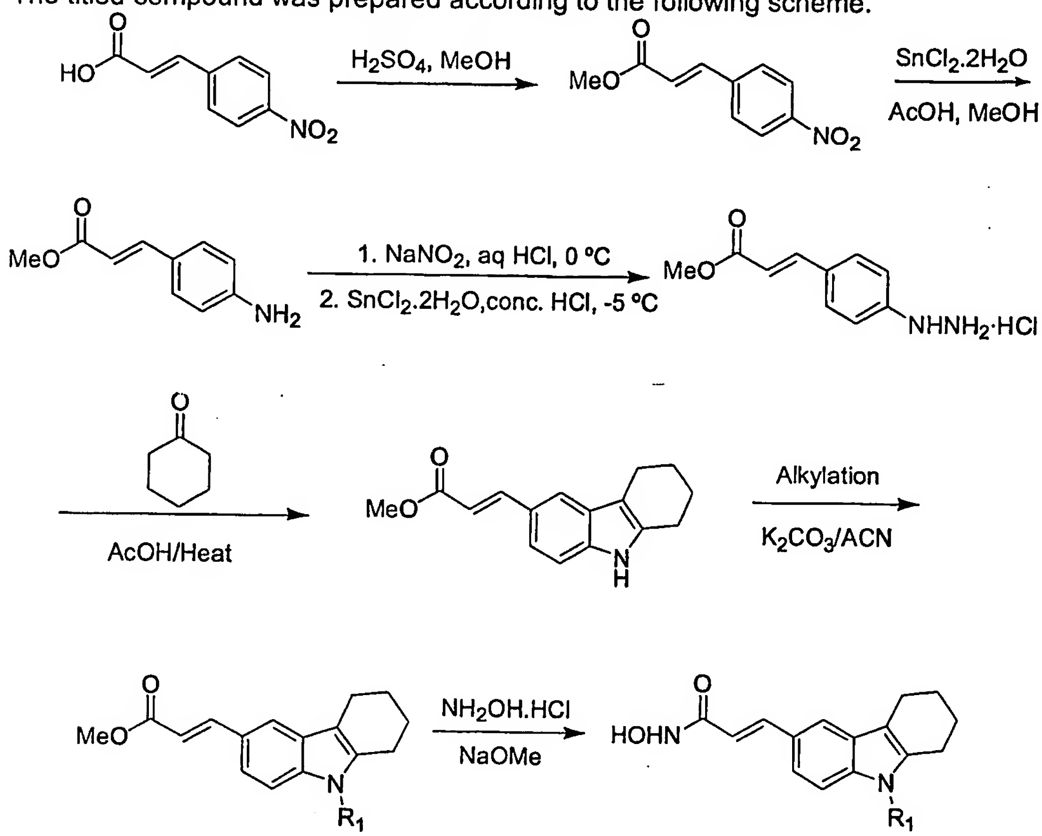
***N*-Hydroxy-3-[1-(2-piperidin-1-yl-ethyl)-2,3-dihydro-1*H*-indol-5-yl]-acrylamide (14)**

To a pre-stirred solution of 126 mg (0.38mmol) of precursor ester, 265 mg (3.8mmol) of hydroxylamine HCl salt in 3 mL of dried MeOH, was added 1.6 mLof sodium methoxide (4.9M in methanol). The resulting solution was stirred at room temperature for 16 hours. The reaction was quenched by adding 1M HCl and purified by HTP. 10mg of product was obtained. Purity 92.9% by HPLC; t_R=(LC/PDA: Xterra 1S column, 4.6 x 20mm 3.5µ column; 2.0 ml/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254). T=1.07min. MS(m/z): 316 $[MH]^+$.

Compounds in which R^2 and R^{2a} form a cyclic group are outlined in the general scheme below. Modification of the starting materials and the reagents allows entry into a wide range of functionalised derivatives. In general the crucial step is the alkylation step which introduces functionality at position R^1. This step can be used to access a wide variety of precursor methyl esters which are then hydrolysed to the desired hydroxamic acid.

Example 15
N-Hydroxy-3-[9-(2-piperidin-1-yl-ethyl)-6,7,8,9-tetrahydro-5H-carbazol-3-yl]-acrylamide
(15)

The titled compound was prepared according to the following scheme.



Step 1

Preparation of 3-(4-Nitro-phenyl)-acrylic acid methyl ester

To a pre-stirred solution of 25g (0.13mol) of 3-(4-Nitro-phenyl)-acrylic acid in 30 mL of methanol, was added 10 mL of Conc. H_2SO_4. The mixture was refluxed for 18 hours. 25g of product 3-(4-Nitro-phenyl)-acrylic acid methyl ester were obtained after silica gel column purification.

Step 2

Preparation of 3-(4-Amino-phenyl)-acrylic acid methyl ester

To a pre-stirred solution of 25g (0.12mol) of 3-(4-Nitro-phenyl)-acrylic acid methyl ester in 180 mL of Conc. HCl, was added 110g (0.49mol) of Tin chloride. The mixture was refluxed for about 1 hour. After cooled down to 0°C, the solid collected by filtration was washed with ether and dried in vacuo. 17g of crude product 3-(4-Amino-phenyl)-acrylic acid methyl ester were obtained (81% yield).

Step 3

Preparation of 3-(4-Hydrazino-phenyl)-acrylic acid methyl ester

To a pre-stirred solution of 4.3g (20mol) of 3-(4-Amino-phenyl)-acrylic acid methyl ester in 30mL of 4M HCl, was added slowly 1.38g (20mol) $NaNO_2$ in H_2O (6mL) at 0°C. The mixture was stirred for 10min, and then was added dropwise to a rapidly stirred solution of 18g (80mol) of Tin chloride in 75mL Conc. HCl at 0°C. After being stirred for another 1 hour, the product was collected by filtration, washed with ether and dried in vacuo. 4.0g of crude product 3-(4-Hydrazino-phenyl)-acrylic acid methyl ester were obtained with the yield of about 90%.

Step 4

Preparation of 3-(6,7,8,9-Tetrahydro-5H-carbazol-3-yl)-acrylic acid methyl ester

To a pre-stirred solution of 460 mg of 3-(4-Hydrazino-phenyl)-acrylic acid methyl ester (20mmol) in 2 mL of acetic acid, 60 uL (30mmol) of cyclohexanone was added. The mixture was refluxed for 2 hours. 78 mg of pure compound 3-(6,7,8,9-Tetrahydro-5H-carbazol-3-yl)-acrylic acid methyl ester was obtained after column purification.

Step 5

Preparation of 3-[9-(2-Dimethylamino-ethyl)-6,7,8,9-tetrahydro-5*H*-carbazol-3-yl]-acrylic acid methyl ester

To a pre-stirred solution of 255mg (1.0mmol) of 3-(6,7,8,9-Tetrahydro-5H-carbazol-3-yl)-acrylic acid methyl ester, 1.15g (8 mmol) of amine in 30 mL of ACN, 1.66g (12 mmol) K_2CO_3 were added. The mixture was heated to 90°C for over weekend. After removing the ACN, the mixture was added DCM and water, collected the organic layer and washed with water twice. 170mg (yield 52%) of compound 3-[9-(2-Dimethylamino-ethyl)-6,7,8,9-tetrahydro-5H-carbazol-3-yl]-acrylic acid methyl ester was obtained after flash chromatography.

Step 6:

Preparation of titled Compound (15)

To a pre-stirred solution of 100 mg (0.27 mmol) of 3-[9-(2-Dimethylamino-ethyl)-6,7,8,9-tetrahydro-5H-carbazol-3-yl]-acrylic acid methyl ester, 279 mg (4.0 mmol)of hydroxylamine HCl salt in 2.0 ml of dried MeOH, was added 1.7 mL of sodium methoxide (4.9M in methanol). The resulting solution was stirred at room temperature for 16 hours. The reaction was quenched by adding 1M HCl and purified by reversed phase HPLC. 10mg of product was obtained. Purity: 99% by HPLC; t_R==(LC/PDA:

Xterra 1S column, 4.6 x 20mm 3.5μ column; 2.0 ml/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 1.78min. MS(m/z): 368 $[MH]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 1.84 (10H, m), 2.64 (2H, m), 2.75 (2H, m), 3.00 (2H, m), 3.28 (4H, m), 4.45 (2H, m), 6.40 (1H, d), 7.34 (1H, d), 7.48 (2H, m), 7.66 (1H, m), 9.80 (1H, bs), 10.61 (1H, bs).

Example 16

3-[1-(2-Dimethylamino-ethyl)-3-isobutyl-2-methyl-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide (16)

To a pre-stirred solution of 110 mg (0.32 mmol) of precursor ester, 332 mg (4.8 mmol) of hydroxylamine HCl salt in 2.0 mLof dried MeOH, was added 2.0 mL of sodium methoxide (4.9M in methanol). The resulting solution was stirred at room temperature for 16 hours. The reaction was quenched by adding 1M HCl and purified by reversed phase HPLC. 34mg of product was obtained. Yield : 31%. Purity: 100% by HPLC:; t_R==(LC/PDA: Xterra 1S column, 4.6 x 20mm 3.5μ column; 2.0 ml/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 1.88min.MS(m/z): 344 $[MH]^+$.^1H NMR (400 MHz, DMSO-d_6) δ 0.84 (6H, d), 1.87 (1H, m), 2.37 (3H, s), 2.50 (2H, m), 2.87 (6H, s), 3.33 (2H, m), 4.49 (2H, m), 6.40 (1H, d), 7.33 (1H, d), 7.48 (1H, m), 7.55 (1H, d), 7.66 (1H, s), 10.14 (1H, bs), 10.65 (1H, bs).

Example 17

3-[9-(2-Dimethylamino-ethyl)-6,7,8,9-tetrahydro-5*H*-carbazol-3-yl]-*N*-hydroxy-acrylamide (17)

To a pre-stirred solution of 170 mg (0.52 mmol) of precursor ester, 540 mg (7.8 mmol) of hydroxylamine HCl salt in 2.0 mLof dried MeOH, was added 3.2 mL of sodium methoxide (4.9M in methanol). The resulting solution was stirred at room temperature for 16 hours. The reaction was quenched by adding 1M HCl and purified by reversed phase HPLC. 20mg of product was obtained (yield: 12%). Purity: 99% by HPLC; t_R==(LC/PDA: Xterra 1S column, 4.6 x 20mm 3.5μ column; 2.0 ml/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 1.78 min.MS(m/z): 368 $[MH]^+$.^1H NMR (400 MHz, DMSO-d_6) δ 1.84 (10H, m), 2.64 (2H, m), 2.75 (2H, m), 3.00 (2H, m), 3.28 (4H, m), 4.45 (2H, m), 6.40 (1H, d), 7.34 (1H, d), 7.48 (2H, m), 7.66 (1H, m), 9.80 (1H, bs), 10.61 (1H).

Example 18

***N*-Hydroxy-3-(3-isobutyl-2-methyl-1*H*-indol-5-yl)-acrylamide(18)**

To a pre-stirred solution of 100 mg (0.37mmol) of precursor ester, 382 mg (5.5 mmol) of hydroxylamine HCl salt in 2.0 mL of dried MeOH, was added 2.3 mL of sodium methoxide (4.9M in methanol). The resulting solution was stirred at room temperature for 16 hours. The reaction was quenched by adding 1M HCl and purified by reversed phase HPLC. 10mg of product was obtained. Purity: 100% by HPLC; t_R==(LC/PDA: Xterra 1S column, 4.6 x 20mm 3.5µ column; 2.0 ml/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B:Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 2.66min. MS(m/z): 273 $[MH]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 0.86 (6H, d), 1.87 (1H, m), 2.37 (3H, s), 2.50 (2H, m), 6.34 (1H, d), 7.21 (2H, m), 7.55 (2H, m), 10.56 (1H, s), 10.88 (1H, s).

Example 19

3-[1-(3-Dimethylamino-2-methyl-propyl)-3-isobutyl-2-methyl-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide (19)

To a pre-stirred solution of 330 mg (0.89mmol) of precursor ester, 615 mg (8.9 mmol) of hydroxylamine HCl salt in 2.0 mL of dried MeOH, was added 5.4 mL of sodium methoxide (4.9M in methanol). The resulting solution was stirred at room temperature for 16 hours. The reaction was quenched by adding 1M HCl and purified by reversed phase HPLC. 60mg of product was obtained (yield: 18%). Purity: 96.7% by HPLC; t_R=(LC/PDA: Xterra 1S column, 4.6 x 20mm 3.5µ column; 2.0 ml/min, gradient 5-95% B over 5 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 2.084min. MS(m/z): 372 $[MH]^+$. ^1H NMR (400 MHz, DMSO-d_6) δ 0.84 (9H, m), 1.87 (1H, m), 2.35 (3H, s), 2.53 (1H, m), 2.72 (3H, s), 2.79 (3H, s), 3.05 (2H, m), 3.99 (2H, m), 4.21 (2H, m), 6.40 (1H, d), 7.33 (1H, d), 7.48 (1H, m), 7.55 (1H, d), 7.66 (1H, s), 10.10 (1H, bs).

Example 20

Preparation of 1-Benzyl-5-(2-hydroxycarbamoyl-vinyl)-1H-indazole-3-carboxylic acid [2-(3,4-dimethoxy-phenyl)-ethyl]-amide (20)

Step 1

Synthesis of intermediate XIX

The intermediate **XIX** was prepared according to the method reported (*J Heterocyclic Chemistry, **1964**, 1(5), 239-241*). To a solution of 0.55 g of sodium hydroxide in 10 mL of water, 3.2 g of 5-bromoisatin (16.9 mmol) was added. After stirring for one hour the

solution was cooled to 5°C and treated, under stirring, with 1.0 g of sodium nitrite dissolved in 40 mL of water. It was then poured, in small portions and with vigorous stirring, into aqueous sulfuric acid (0.8 mL of acid, d=1.84, in 30 mL of water) cooled at 0°C, and sulfur dioxide was bubbled through until most of the yellow precipitate which had formed was dissolved. The golden-yellow liquid obtained after filtration was poured into a solution of 4.8 g of stannous chloride in 10 mL of hydrochloric acid, and the mixture left for 5 hours at room temperature. The precipitate obtained was collected, washed thoroughly with dilute hydrochloric acid, then with water, to give a yellow solid crude product <u>XIX</u> (1.4 g, 30% yield). LC-MS (ESI, positive mode): [MH]+ = 241, 243

<u>Step 2</u>

Synthesis of amide XX

To a solution of carboxylic acid <u>XIX</u> (1.0 g, 4.1 mmol) in DCM (30 mL) was added pyBop (4.2 g, 8.2 mmol) and DIEA (1.1 g, 8.2 mmol). The mixture was stirred for one hour, then the amine component 2-(3,4-dimethoxyphenyl)ethylamine (0.84 mL, 4.92 mmol) was added. The reaction mixture was stirred overnight, then was filtered through silica gel (10 g) to give a yellow solid crude product <u>XX</u> (1.1 g, 68% yield). LC-MS (ESI, positive mode): $[MH]^+$ = 404, 406

<u>Step 3</u>

Synthesis of *N*-alkylated indazole

To a solution of amide <u>XX</u> (0.7 g, 1.7 mmol) in acetonitrile (10 mL) was added potassium carbonate (20 mg) and benzyl bromide (0.8 mL, 6.8 mmol). The reaction mixture was stirred at 50°C overnight and the product was purified by HPLC to give an yellow oily product <u>XXI</u> (100 mg, 15% yield). LC-MS (ESI, positive mode): $[MH]^+$ = 494, 496

<u>Step 4</u>

Heck Reaction

To a solution of amide <u>XXI</u> (100 mg, 0.22 mmol) in DMF (5.0 mL) was added ethyl acrylate <u>XXIII</u> (0.12 mL, 1.1 mmol), $Pd[Ph_3P]_4$ (25 mg), Ph_3P (5 mg), and DIEA (55 uL). The reaction mixture was stirred at 110°C under nitrogen atmosphere for 4 h. The product <u>XXIV</u> was purified by HPLC and isolated as an yellow oil (40 mg). LC-MS (ESI, positive mode): $[MH]^+$ = 514.

<u>Step 5</u> Hydroxamic acid formation

To a solution of carboxylic ester **XXIV** (40 mg, 0.078 mmol) in methanol (2.0 mL) was added hydroxylamine hydrochloride (53.7 mg, 0.78 mmol) and sodium methoxide in

methanol (0.26 mL, 4.37M). The reaction mixture was stirred at room temperature for 12 h. After HPLC purification the product was lyophilised to give the expected hydroxamate (**XXV**) as a white powder (7.0 mg, 17% yield). LC-MS (ESI, positive mode): [MH]+ = 501.6; ^{1}H NMR (DMSO-d_6) δ 2.80 (t, J=7.72 Hz, 1H), 3.51 (m, 2H), 3.67 & 3.68 (2s, 6H, OCH_3), 5.71 (s, 2H), 6.49 (d, J=15.76 Hz, 1H), 6.74-6.77 (m, 1H), 6.83-6.85 (m, 3H), 7.22-7.34 (m, 6H), 7.55 (d, J=15.80 Hz, 1H), 7.67 (d, J=8.56 Hz, 1H), 7.77 (d, J=8.88 Hz, 1H), 8.31 (s, 1H), 8.44 (t, J=5.76 Hz, 1H);^{13}C NMR (DAPT135, DMSO-d_6)δ 34.6 (3 CH_2), 40.1, 52.4, 55.2, 55.4, 111.1, 111.7, 112.4, 118.1, 120.5, 121.7, 126.0, 127.2, 127.8, 128.6, 138.6

Example 21

<u>*N*-hydroxy-3-[3-(3-hydroxyl-propyl)-2-phenethyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl]-acrylamide (21)</u>

<u>Step 1</u>

To a round-bottom flask charged with 5-Bromo-3-nitro-pyridin-2-ol (976 mg, 4.0 mmol) was added 6.0 mL of phosphoryl chloride, the resulting suspension was heated to 105 °C and kept for 12 hrs. Then the excess $POCl_3$ was removed under reduced pressure, the residue then was dissolved in anhydrous 10 mL of DCM, 1mL of 3-aminopropyl-1-ol was then added. The resulting mixture was stirred for 30 min., DCM was then removed under reduced pressure to give a oil residue which was stirred at 45 °C for 12 hrs. Then the reaction was quenched with water, extracted with ethyl acetate, washed with brine and dried over sodium sulfate. After removal of solvent, the residue was obtained as a yellow solid 3-(5-bromo-3-nitro-pyridin-2-ylamino)-propan-1-ol and was used for next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (2H, m), 2.60 (1H, br.), 3.71 (2H, m), 3.78 (2H, m), 8.42 (1H, d, J = 2.4 Hz), 8.55 (1H, d, J = 2.4 Hz); MS m/z $(MH)^+$: 276, 278

<u>Step 2</u>

To a solution of 3-(5-bromo-3-nitro-pyridin-2-ylamino)-propan-1-ol (556 mg, 2.0 mmol) in 20 mL of MeOH and AcOH mixture (1:9) was added phenylpropylaldehyde (0.79 mL, 6.0 mmol) and tin chloride (2.26 g, 10 mmol), the resulting mixture was stirred at 45 °C for 24 hrs. Then the mixture was diluted using ethyl acetate (200 mL) at room temperature, and was then quenched with sat. sodium carbonate. The resulting mixture was stirred for additional 1 hour, then extracted with ethyl acetate, washed with brine and dried over sodium sulfate. After removal of solvent under reduced pressure, the residue was purified on column (hexanes:EtOAc = 2:1) to give a pale-yellow solid 3-(6-Bromo-2-phenethyl-1,2-dihydro-imidazo[4,5-*b*]pyridin-3-yl)-propan-1-ol (501 mg,

71%), which is unusually stable. Then this product (362 mg, 1.0 mmol) was dissolved in 4 mL of DMF and was added Oxone (615 mg, 1.0 mmol). The resulting mixture was stirred for 2 hrs., was then quenched with sat. sodium carbonate, extracted with ethyl acetate, washed with brine and dried over sodium sulfate. After removal of solvent under reduced pressure, the residue was obtained as a white solid 3-(6-Bromo-2-phenethyl-imidazo[4,5-*b*]pyridin-3-yl)-propan-1-ol (360 mg, 100%), which is pure enough for next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (2H, m), 2.95-3.38 (6H, m), 3.95 (1H, br.), 4.27 (2H, t, J = 6.0 Hz), 7.20-7.35 (5H, m), 8.19 (1H, d, J = 2.4 Hz), 8.37 (1H, d, J = 2.4 Hz);MS m/z $(MH)^+$: 360, 362

Step 3

To a solution of $Pd(OAc)_2$ (6.3 mg, 0.028 mmol) and PPh_3 (15.7 mg, 0.06 mmol) in 5 mL of DMF was added compound 3-(6-Bromo-2-phenethyl-imidazo[4,5-*b*]pyridin-3-yl)-propan-1-ol (100 mg, 0.28 mmol) and ethyl acrylate (0.3 mL, 2.8 mmol) and DIEA (0.09 mL, 1.0 mmol) at room temperature under nitrogen. The resulting mixture was then stirred at 110 °C for 4 hrs. LC/MS showed that there is no more starting material left. After work-up, the residue was then purified on column (Hexanes:EtOAc = 1:1) to give 35 mg of pure product 3-[3-(3-hydroxyl-propyl)-2-phenethyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl]-acrylic acid ethyl ester (33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H, t, J = 7.2 Hz), 1.84 (2H, m), 3.20-3.40 (6H, m), 4.28-4.35 (5H, m), 6.54 (1H, d, J = 16.0 Hz), 7.20-7.35 (5H, m), 7.85 (1H, d, J = 16.0 Hz), 8.21 (1H, d, J = 2.4 Hz), 8.46 (1H, d, J = 2.4 Hz); MS m/z $(MH)^+$: 380

Step 4

To a suspension of above ethyl ester (38 mg, 0.1 mmol) in 0.3 mL of MeOH was added a pre-prepared 2.0 M NH_2OH in MeOH solution (1.0 mL, 2.0 mmol). The resulting suspension was stirred for 4 hrs. then quenched with TFA (0.2 mL, 2.6 mmol). The resulting solution was purified on preparative HPLC to give 10 mg of *N*-hydroxy-3-[3-(3-hydroxyl-propyl)-2-phenethyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl]-acrylamide (**21**) (yield: 26%), Purity: 99% on HPLC; t_R=(LC/PDA: Phenomenex Luna C18 2.0x150mm 5μ column; 0.8 mL/min, gradient 5-95% B over 20 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 4.35 min. ^{1}H NMR (400 MHz, MeOD) δ 1.95 (2H, m), 3.18 (2H, t, J = 7.2 Hz), 3.41-3.51 (4H, m), 4.35 (2H, t, J = 7.2 Hz), 6.59 (1H, d, J = 16.0 Hz), 7.14-7.25 (5H, m), 7.68 (1H, d, J = 16.0 Hz), 8.22 (1H, s), 8.64 (1H, s); MS m/z $(MH)^+$: 367

Example 22

3-(3-Benzyl-2-phenethyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-hydroxy-acrylamide (22)

The titled compound (**22**) was prepared according to the procedures described in Example 21, by using appropriate starting materials. Purity: 95 % by HPLC; t_R=(LC/PDA: Phenomenex Luna C18 2.0x150mm 5μ column; 0.8 mL/min, gradient 5-95% B over 20 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 7.15 min. ^{1}H NMR (400 MHz, DMSO) δ 2.95 (2H, m), 3.12 (2H, m), 5.46 (2H, s), 6.52 (1H, d, *J* = 16.0 Hz), 7.05- 7.50 (10H, m), 7.58 (1H, d, *J* = 16.0 Hz), 8.21 (1H, s), 8.52 (1H, s); MS m/z $(MH)^+$: 399

Example 23

***N*-hydroxy-3-[2-phenethyl-3-(2-piperidin-1-yl-ethyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl]-acrylamide (23)**

The titled compound (**23**) was prepared according to the procedures described in Example 21, by using appropriate starting materials. Purity: 95 % by HPLC; t_R=(LC/PDA: Phenomenex Luna C18 2.0x150mm 5μ column; 0.8 mL/min, gradient 5-95% B over 20 min, Solvent A: H_2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 4.42 min. ^{1}H NMR (400 MHz, MeOD) δ 1.46 (1H, m), 1.68-1.90 (5H, m), 2.90 (2H, m), 3.10-3.70 (6H, m), 3.67 (2H, m), 4.48 (2H, t, *J* = 6.0 Hz), 6.46 (1H, d, *J* = 16.0 Hz), 7.10-7.25 (5H, m), 7.58 (1H, d, *J* = 16.0 Hz), 8.15 (1H, s), 8.44 (1H, s); MS m/z $(MH)^+$: 420

Example 24

Preparation of 3-[2-Butyl-3-(2-diethylamino-ethyl)-3*H*-imidazo[4,5-*b*]pyridine-6-yl]-*N*-hydroxy-acrylamide (24)

The titled compound was prepared according to the procedures described in Example 21, by suing appropriate starting materials. Purity: 90% by HPLC; t_R=(LCP/DA: Phenomenex Luna C18 2.0X150mm 5 μ column; 0.8 mL/min; gradient 5-95% B over 10 min. Solvent A: H2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 0.88 min. ^{1}H NMR (400 MHz, CD_3OD) δ 0.97 (3H, t, J = 7.28 Hz), 1.31 (6H, t, J = 7.28 Hz), 1.51 (2H, m), 1.86 (2H, m), 3.67 (2H, t, J = 7.36 Hz), 4.72 (4H, m), 6.52 (1H, d, J = 15.76 Hz), 7.64 (2H, d, J = 15.80 Hz), 8.23 (1H, s), 8.51 (1H, s). MS m/z $(MH)^+$: 360

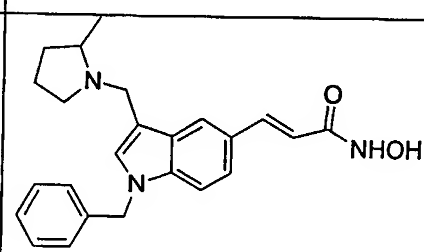
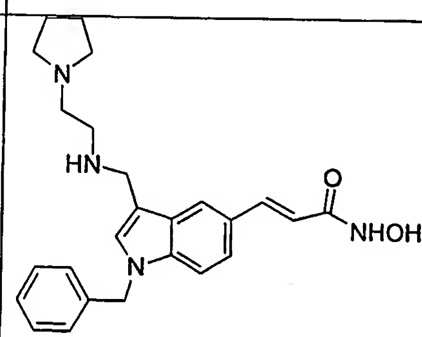
Example 25

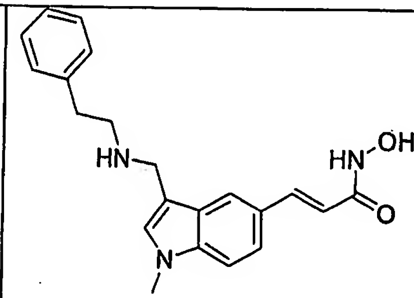
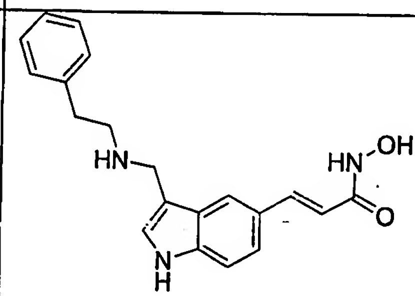
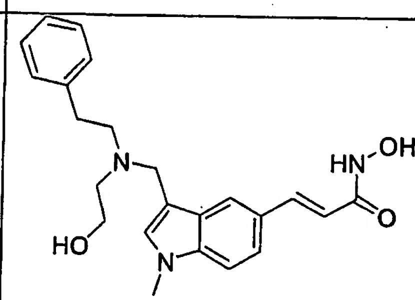
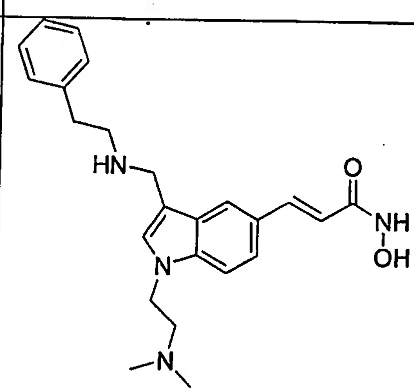
Preparation of 3-[2-Butyl-3-(3-dimethylamino-2,2-dimethyl-propyl)-3*H*-imidazo[4,5-*b*]pyridine-6-yl]-*N*-hydroxy-acrylamide (25)

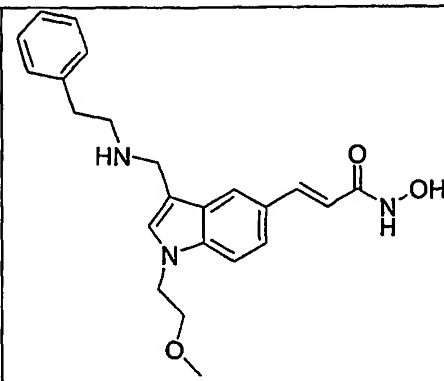
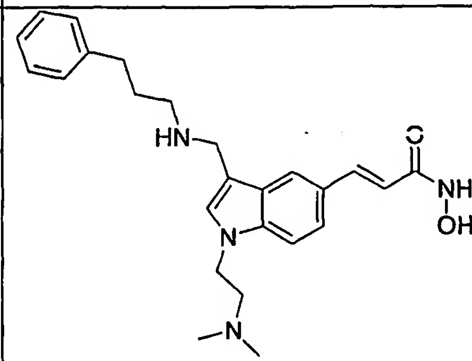
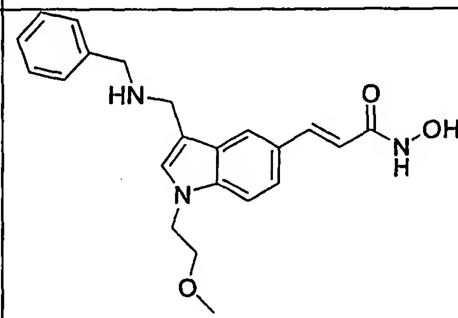
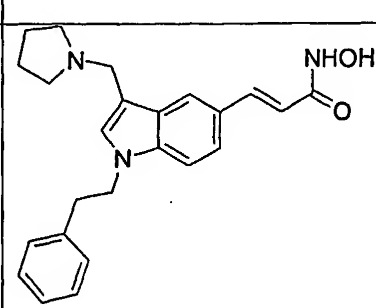
The titled compound was prepared according to the procedures described in Example 21, by using appropriate starting materials. Purity: 98% by HPLC; t_R=(LCP/DA: Phenomenex Luna C18 2.0X150mm 5 µ column; 0.8 mL/min, gradient 5-95% B over 10 min, Solvent A: H2O with 0.1% trifluoroacetic acid; Solvent B: Acetonitrile with 0.1% trifluoroacetic acid; UV 254): 0.91 min. (400 MHz, CD_3OD) δ 0.97 (3H, t, J = 7.32 Hz), 1.21 (6H, s), 1.47 (2H, m, J = 7.60 Hz), 1.88 (2H, m, J = 7.56 Hz), 3.07 (2H, m, J = 7.40 Hz), 3.20 (2H, s), 4.40 (2H, s), 6.58 (2H, d, J = 15.80 Hz), 7.65 (2H, d, J = 15.80 Hz). 8.23 (1H, s), 8.58 (1H, s). MS m/z $(MH)^+$: 374

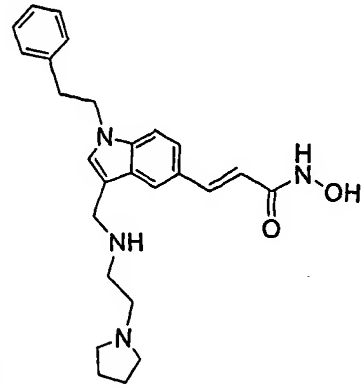
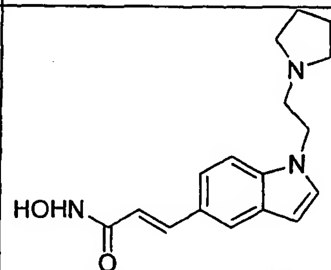
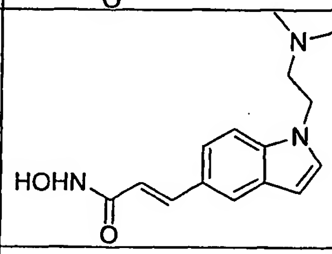
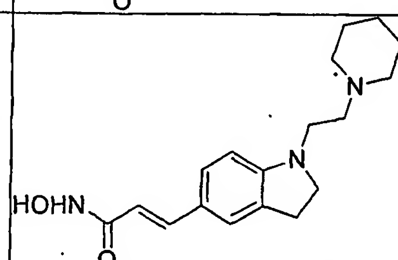
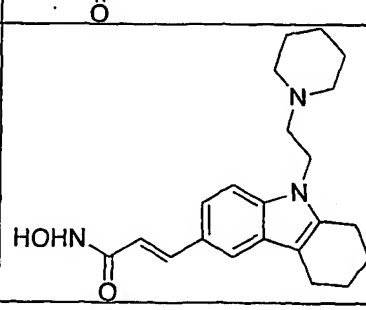
The following compounds are some representative examples prepared by methods disclosed or analogous to those disclosed in the above examples.

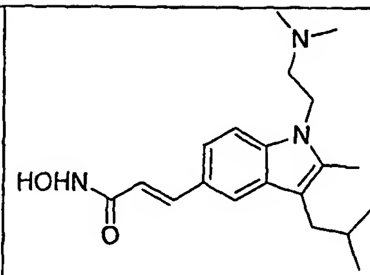
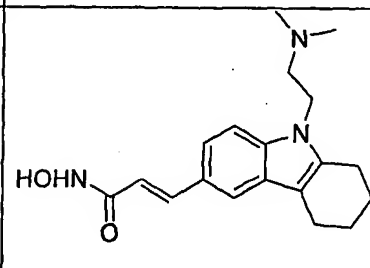
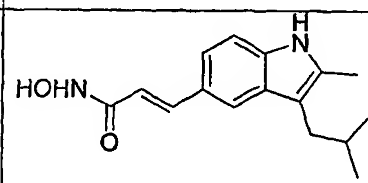
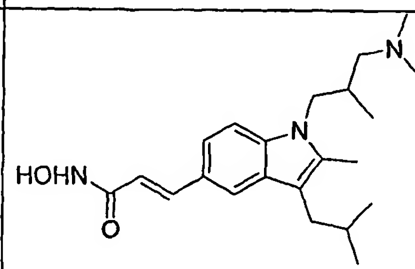
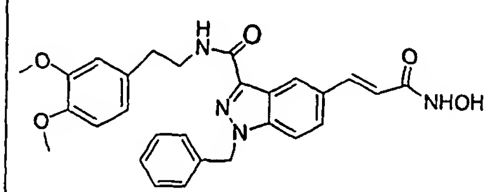
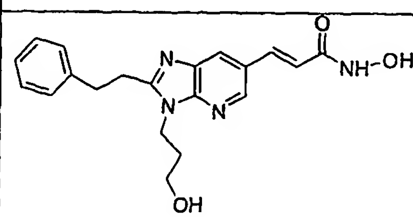
Table 1

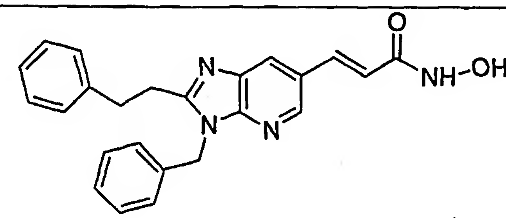
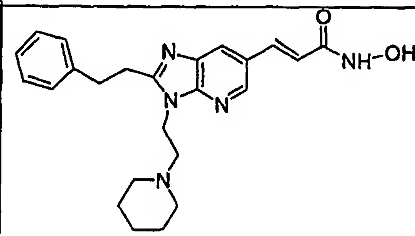
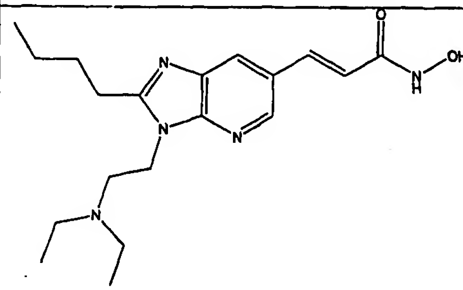
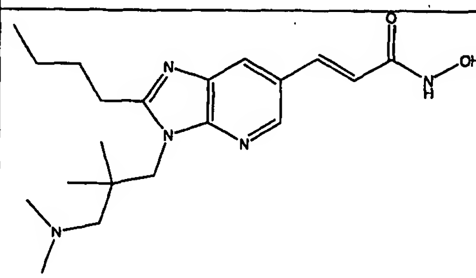
Cmpd No.	Compound name	Structure	Ms (m/z) $[MH]^+$
1	3-[1-Benzyl-3-(2-methyl-pyrrolidin-1-ylmethyl)-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide		390
2	3-{1-Benzyl-3-[(2-pyrrolidin-1-yl-ethylamino)-methyl]-1*H*-indol-5-yl}-*N*-hydroxy-acrylamide		419

3	*N*-Hydroxy-3-[1-methyl-3-(phenethylamino-methyl)-1*H*-indol-5-yl]-acrylamide		350
4	*N*-Hydroxy-3-[3-(phenethylamino-methyl)-1*H*-indol-5-yl]-acrylamide		336
5	*N*-Hydroxy-3-(3-{[(2-hydroxy-ethyl)-phenethyl-amino]-methyl}-1-methyl-1*H*-indol-5-yl)-acrylamide		394
6	3-[1-(2-Dimethylamino-ethyl)-3-(phenethylamino-methyl)-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide		407

7	*N*-Hydroxy-3-[1-(2-methoxy-ethyl)-3-(phenethylamino-methyl)-1*H*-indol-5-yl]-acrylamide		394
8	3-{1-(2-Dimethylamino-ethyl)-3-[(3-phenyl-propylamino)-methyl]-1*H*-indol-5-yl}-*N*-hydroxy-acrylamide		421
9	3-[3-(Benzylamino-methyl)-1-(2-methoxy-ethyl)-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide		380
10	*N*-Hydroxy-3-(1-phenethyl-3-pyrrolidin-1-ylmethyl-1*H*-indol-5-yl)-acrylamide		390

11	*N*-Hydroxy-3-{1-phenethyl-3-[(2-pyrrolidin-1-yl-ethylamino)-methyl]-1*H*-indol-5-yl}-acrylamide		432
12	*N*-Hydroxy-3-[1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indol-5-yl]-acrylamide		300
13	3-[1-(2-Dimethylamino-ethyl)-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide		274
14	*N*-Hydroxy-3-[1-(2-piperidin-1-yl-ethyl)-2,3-dihydro-1*H*-indol-5-yl]-acrylamide		316
15	*N*-Hydroxy-3-[9-(2-piperidin-1-yl-ethyl)-6,7,8,9-tetrahydro-5*H*-carbazol-3-yl]-acrylamide		368

16	3-[1-(2-Dimethylamino-ethyl)-3-isobutyl-2-methyl-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide		344
17	3-[9-(2-Dimethylamino-ethyl)-6,7,8,9-tetrahydro-5*H*-carbazol-3-yl]-*N*-hydroxy-acrylamide		328
18	N-Hydroxy-3-(3-isobutyl-2-methyl-1H-indol-5-yl)-acrylamide		273
19	3-[1-(3-Dimethylamino-2-methyl-propyl)-3-isobutyl-2-methyl-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide		372
20	1-Benzyl-5-(2-hydroxycarbamoyl-vinyl)-1*H*-indazole-3-carboxylic acid [2-(3,4-dimethoxy-phenyl)-ethyl]-amide		501
21	*N*-hydroxy-3-[3-(3-hydroxyl-propyl)-2-phenethyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl]-acrylamide		367

22	3-(3-Benzyl-2-phenethyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-hydroxy-acrylamide		399
23	*N*-hydroxy-3-[2-phenethyl-3-(2-piperidin-1-yl-ethyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl]-acrylamide		420
24	3-[2-Butyl-3-(2-diethylamino-ethyl)-3*H*-imidazo[4,5-b]pyridin-6-yl]-*N*-hydroxy-acrylamide		360
25	3-[2-Butyl-3-(3-dimethylamino-2,2-dimethyl-propyl)-3*H*-imidazo[4,5-b]pyridin-6-yl]-*N*-hydroxy-acrylamide		374

BIOLOGICAL TESTING AND ENZYME ASSAYS

Recombinant GST-HDAC Protein expression and purification

Human cDNA library was prepared using cultured SW620 cells. Amplification of human HDAC1 and HDAC8 coding region from this cDNA library was cloned separately into the baculovirus expression pDEST20 vector and pFASTBAC vector respectively (GATEWAY Cloning Technology, Invitrogen Pte Ltd). The pDEST20-HDAC1 and pFASTBAC-HTGST-HDAC8 constructs were confirmed by DNA sequencing. Recombinant baculovirus was prepared using the Bac-To-Bac method following the manufacturer's instruction (Invitrogen Pte Ltd). Baculovirus titer was determined by plaque assay to be about 10_8 PFU/ml.

Expression of GST-HDAC1 or HTGST-HDAC8 was done by infecting SF9 cells (Invitrogen Pte Ltd) with pDEST20-HDAC1 or pFASTBAC-GST-HDAC8 baculovirus at MOI=1 for 48 h. Soluble cell lysate was incubated with pre-equilibrated Glutathione Sepharose 4B beads (Amersham) at 4°C for 2 h. The beads were washed with PBS buffer for 3 times. The GST-HDAC1 protein or GST-HDAC8 protein was eluted by elution buffer containing 50 mM Tris, pH8.0, 150mM NaCl, 1% Triton X-100 and 10mM or 20mM reduced Glutathione. The purified GST-HDAC1 protein or purified GST-HDAC8 protein was dialyzed with HDAC storage buffer containing 10mM Tris, pH7.5, 100mM NaCl and 3mM $MgCl_2$. 20% Glycerol was added to purified GST-HDAC1 protein or purified GST-HDAC8 before storage at -80°C.

***In vitro* HDAC assay for determination of IC_{50} values**

The assay has been carried out in 96 well format and the BIOMOL fluorescent-based HDAC activity assay has been applied. The reaction composed of assay buffer, containing 25 mM Tris pH 7.5, 137 mM NaCl, 2.7 mM KCl, 1 mM $MgCl_2$, 1 mg/ml BSA, tested compounds, an appropriate concentration of HDAC8 enzyme or HDAC1 enzyme, 200 µM *Flur de lys* p53 peptide substrate for HDAC8 enzyme or 500 µM *Flur de lys* generic substrate for HDAC1 enzyme and subsequently was incubated at room temperature for 2 h. *Flur de lys* Developer was added and the reaction was incubated for 10 min. Briefly, deacetylation of the substrate sensitizes it to the developer, which then generates a fluorophore. The fluorophore is excited with 360 nm light and the emitted light (460 nm) is detected on a fluorometric plate reader (Tecan Ultra Microplate detection system, Tecan Group Ltd).

The analytical software, Prism 3.0 (GraphPad Software Inc) has been used to generate IC_{50} from a series of data. The HDAC enzyme inhibition results of representative compounds are shown in Table 2 ((unit in the table is micromolar).

Table 2

Cmpd No.	IC_{50}(HDAC1) μM	IC_{50}(HDAC8) μM	Cmpd No.	IC_{50}(HDAC1) μM	IC_{50}(HDAC8) μM
1	6.3	0.60	14	0.43	
2	1.1	0.39	15	0.50	
3	6.5	0.54	16	3.0	
4	3.5	0.35	17	0.83	
5	0.98	0.23	19	4.2	
6	1.9	0.24	20	0.19	
7	3.3	0.22	21	0.26	
8	0.51	0.28	22	0.56	
9	3.0	0.13	23	0.51	
11	2.9	0.47	24	0.23	
12	0.17		25	1.3	
13	0.24				

Ceii-based proliferation assay for determination of GI_{50} values

Human cancer cell lines (e.g. Colo205) were obtained from ATCC. Colo205 cells were cultivated in RPMI 1640 containing 2 mM L-Glutamine, 5% FBS, 1.0 mM Na Pyruvate. Colo205 cells were seeded in 96-wells plate at 5000 cells per well. The plates were incubated at 37°C, 5% CO_2, for 24 h. Cells were treated with compounds at various concentrations for 96 h. Cell growth was then monitored using CyQUANT® cell proliferation assay (Invitrogen Pte Ltd). Dose response curves were plotted to determine GI_{50} values for the compounds using XL-fit (ID Business Solution, Emeryville, CA).

The cellular or growth inhibition activity results of representative compounds are shown in Table 3 (unit in the table is micromolar). The data indicated that the compounds of this invention are active in the inhibition of tumor cell growth.

Table 3

Compound No.	GI_{50} (Colo205) μM	Compound No.	GI_{50} (Colo205) μM
3	13	16	3.3
4	24	17	4.7
5	6.4	18	3.4
8	2.4	19	7.1
9	17	20	1.6
10	11	21	8.8
11	7.3	22	2.8
12	1.7	23	2.5
13	2.1	24	4.6
14	2.6	25	9.4
15	1.6		

Histone acetylation assay

A hallmark of histone deacetylase (HDAC) inhibition is the increase in the acetylation level of histones. Histone acetylation, including H3, H4 and H2A can be detected by immuno-blotting (western-blot). Colo205 cells, approximately 5 x10^5 cells, were seeded in the previously described medium, cultivated for 24 h and subsequently treated with HDAC inhibitory agents and a positive control at 10 μM final concentration. After 24 h, cells were harvested and lysed according to the instruction from Sigma Mammalian Cell Lysis Kit. The protein concentration was quantified using BCA method (Sigma Pte Ltd). The protein lysate was separated using 4-12% bis-tris SDS-PAGE gel (Invitrogen Pte Ltd) and was transferred onto PVDF membrane (BioRad Pte Ltd). The membrane was probed using primary antibody specific for acetylated histone H3 (Upstate Pte Ltd). The detection antibody, goat anti rabbit antibody conjugated with HRP was used according to the manufacturing instruction (Pierce Pte Ltd). After removing the detection antibody from the membrane, an enhanced chemiluminescent substrate for detection of HRP (Pierce Pte Ltd) was added onto the membrane. After removing the substrate, the membrane was exposed to an X-ray film (Kodak) for 1 sec – 20 mins. The X-ray film was developed using the X-ray film processor. The density of each band observed on the developed film could be qualitatively analyzed using UVP Bioimaging software (UVP, Inc, Upland, CA). The values were then normalized against the density of actin in the corresponding samples to obtain the expression of the protein.

The result of the immuno-blotting assay using acetylated histone H3 antibody are shown in Table 4 for representative compounds of this invention.

Table 4:

Compound No.	Histone Acetylation Activities (Histone-3)	Compound No.	Histone Acetylation Activities (Histone-3)
8	active	15	active
9	active	20	active
10	active	22	active
12	active	23	active
13	active		

These data demonstrate that compounds of this invention inhibit histone deacetylases, thereby resulting in the accumulation of acetylated histones such as H3.

Tumor xenograft model - In vivo antineoplastic (or anti-tumor) effect:

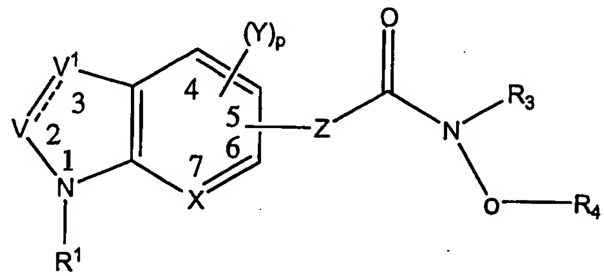
The efficacy of the compounds of the invention can then be determined using tumor xenograft studies. The tumor xenograft model is one of the most commonly used in vivo cancer models.

In these studies Female athymic nude mice (Harlan), 12-14 weeks of age will be implanted subcutaneously in the flank with 5 x 10^6 cells of HCT116 human colon cancer cells, or with 5 x 10^6 cells of A2780 human ovarian cancer cells, or with 5 x 106 cells of PC3 prostate cancer cells. When the tumor reaches the size 100 mm^3, the xenograft nude mice will be paired-match into various treatment groups. The selected HDAC inhibitors will be dissolved in appropriate vehicles and administered to xenograft nude mice intraperitonelly or orally daily for 21 days. The dosing volume will be 0.01 ml/ g body weight. Paclitaxol, which can be used as positive control, will be prepared for intravenous administration in an appropriate vehicle. The dosing volume for Paclitaxol will be 0.01 ml/g body weight. Tumor volume will be calculated every second day or twice-a-week of post injection using the formula: Volume (mm^3) = (w^2 x l)/2, where w = width and l = length in mm of an HCT116, or A2780, or PC3 tumor. Compounds of this invention that are tested will show significant reduction in tumor volume relative to controls treated with vehicle only. Acetylated histone relative to vehicle treated control group when measured shall be accumulated. The result will therefore indicate that compounds of this invention are efficacious in treating a proliferative disease such as cancer.

The details of specific embodiments described in this invention are not to be construed as limitations. Various equivalents and modifications may be made without departing from the essence and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

What is claimed is:

1. A compound of the formula (I):



Formula (I)

wherein

the bond between V and V^1 is a single or a double bond;

(a) when the bond between V and V^1 is a double bond then
V is CR^2 or N;
V^1 is CR^{2a} or N;

wherein V and V^1 are not both N, and further wherein if V^1 is N then X is N;

(b) when the bond between V and V^1 is a single bond then
V is $CR^2{}_2$ or NR^2;
V^1 is $CR^{2a}{}_2$ or NR^2;

X is N or CY;

R^1 is selected from the group consisting of: H, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, arylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynyloxy, cycloalkylkoxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, arylalkyloxy, phenoxy, benzyloxy, amino, alkylamino, aminoalkyl, acylamino, arylamino, sulfonylamino, sulfinylamino, COOH, COR^6, $COOR^6$, $-CONHR^6$, $-NHCOR^6$, $-NHCOOR^6$, $-NHCONHR^6$, $C(=NOH)R^6$, $-alkylNCOR^6$, alkoxycarbonyl, alkylaminocarbonyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, aminosulfonyl, SR^7 and acyl, each of which may optionally be substituted,

or $R^1 = L$,

or R^1 is a group of the formula:

$$-(CR^{20}R^{21})_m-(CR^{22}R^{23})_n-(CR^{24}R^{25})_o-NR^{26}R^{27};$$

wherein each R^{20}, R^{21}, R^{22}, R^{23}, R^{24} and R^{25} is independently selected from the group consisting of: H, halogen, -CN, $-NO_2$, $-CF_3$, $-OCF_3$, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, arylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkoxyheteroaryl, alkenyloxy, alkynyloxy, cycloalkylkoxy, heterocycloalkyloxy, aryloxy, arylalkyloxy, phenoxy, benzyloxy heteroaryloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, alkoxycarbonyl, alkylaminocarbonyl, sulfonyl, alkylsulfonyl, aminosulfonyl, arylsulfonyl, arylsulfinyl -COOH, $-C(O)OR^5$, $-COR^5$, -SH, $-SR^6$, $-OR^6$ and acyl, each of which may be optionally substituted, or

R^{20} and R^{21} when taken together may form a group of formula =O or =S, and/or

R^{22} and R^{23} when taken together may form a group of formula =O or =S, and/or

R^{24} and R^{25} when taken together may form a group of formula =O or =S;

each R^{26} and R^{27} is independently selected from the group consisting of: H, halogen, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, arylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynyloxy, cycloalkylkoxy, heterocycloalkyloxy, aryloxy, arylalkyloxy, heteroaryloxy, amino, alkylamino, aminoalkyl, acylamino, arylamino, phenoxy, benzyloxy, COOH, alkoxycarbonyl, alkylaminocarbonyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, aminosulfonyl, SR^5 and acyl, each of which may be optionally substituted,

or R^{26} and R^{27}, together with the nitrogen atom to which they are attached form an optionally substituted heterocycloalkyl group;

m, n and o are integers independently selected from the group consisting of 0, 1, 2, 3 and 4;

R^2 is selected from the group consisting of: H, halogen, -CN, -NO_2, -CF_3, -OCF_3, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, arylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynyloxy, cycloalkylkoxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, arylalkyloxy, phenoxy, benzyloxy, amino, alkylamino, aminoalkyl, acylamino, arylamino, sulfonylamino, sulfinylamino, -COOH, -COR^6, -$COOR^6$, -$CONHR^6$, -$NHCOR^6$, -$NHCOOR^6$, -$NHCONHR^6$, C(=NOH)R^6, -alkylNCOR^6, alkoxycarbonyl, alkylaminocarbonyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, aminosulfonyl, SR^7 and acyl, each of which may optionally be substituted,
or R^2 = L;

R^{2a} is selected from the group consisting of: H, halogen, -CN, -NO_2, -CF_3, -OCF_3, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, heteroalkyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylalkenyl, cycloalkylheteroalkyl, arylheteroalkyl, heterocycloalkylheteroalkyl, heteroarylheteroalkyl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkenyloxy, alkynyloxy, cycloalkylkoxy, heterocycloalkyloxy, aryloxy, heteroaryloxy, arylalkyloxy, phenoxy, benzyloxy, amino, alkylamino, aminoalkyl, acylamino, arylamino, sulfonylamino, sulfinylamino, -COOH, -COR^6, -$COOR^6$, -$CONHR^6$, -$NHCOR^6$, -$NHCOOR^6$, -$NHCONHR^6$, C(=NOH)R^6, -alkylNCOR^6, alkoxycarbonyl, alkylaminocarbonyl, sulfonyl, alkylsulfonyl, alkylsulfinyl, arylsulfonyl, arylsulfinyl, aminosulfonyl, SR^7 and acyl, each of which may optionally be substituted,
or R^{2a} = L;

or R^2 and R^{2a} are joined such that when taken together with the two carbons to which they are attached they form a cyclic moiety;

each Y is independently selected from the group consisting of: H, halogen, -CN, -NO_2, -CF_3, -OCF_3, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, haloalkynyl, heteroalkyl,

cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, hydroxy, hydroxyalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkoxyheteroaryl, alkenyloxy, alkynyloxy, cycloalkyloxy, cycloalkenyloxy, heterocycloalkyloxy, heterocycloalkenyloxy, aryloxy, heteroaryloxy, arylalkyl, heteroarylalkyl, arylalkyloxy, amino, alkylamino, acylamino, aminoalkyl, arylamino, sulfonyl, alkylsulfonyl, arylsulfonyl, aminosulfonyl, aminoalkyl, alkoxyalky, -COOH –C(O)OR^6, -COR^6, -SH, -SR^7, -OR^7, acyl and –NR^{7}R^8, each of which may be optionally substituted;

p is an integer selected from 0, 1 or 2,

R^3 is selected from the group consisting of H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl each of which may be optionally substituted;

R^4 is selected from the group consisting of: H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl each of which may be optionally substituted;

Each R^5 is independently selected from the group consisting of: H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl each of which may be optionally substituted;

Each R^6 is independently selected from the group consisting of: H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl and acyl each of which may be optionally substituted;

Each R^7 and R^8 is independently selected from the group consisting of: H, alkyl, alkenyl, alkynyl, haloalkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, cycloalkylalkyl, heterocycloalkylalkyl, arylalkyl, heteroarylalkyl, arylheteroalkyl, heteroarylheteroalkyl, and acyl each of which may be optionally substituted;

L is selected from the group consisting of:

a) L=Cy-L^1-W-

wherein

Cy is C_1-C_{15} alkyl, aminoalkyl, heteroalkyl heterocycloalkyl, cycloalkyl, aryl, aryloxy or heteroaryl, each of which may be optionally substituted;

L^1 is selected from the group consisting of C_1-C_5 alkyl or C_2-C_5 alkenyl each of which may be optionally substituted;

W is selected from the group consisting of a bond, -O-, -S-, -S(O)-, -S(O)$_2$-, -N(R^9)-, -C(O)N(R^9)-, -SO$_2$N(R^9)-, -N(R^9)C(O)-, -N(R^9)SO$_2$-, and –N(R^9)-C(O)-N(R^{10})-;

b) L=Cy-L^1-W-L^2

wherein,

Cy is C_1-C_{15} alkyl, aminoalkyl, heterocycloalkyl, cycloalkyl, aryl, aryloxy or heteroaryl, each of which may be optionally substituted;

L^1 and L^2 are the same or different and are independently C_1-C_5 alkyl or C_2-C_5 alkenyl each of which may be optionally substituted;

W is selected from the group consisting of a bond, -O-, -S-, -S(O)-,

-S(O)$_2$-, -N(R^9)-, -C(O)N(R^9)-, -SO$_2$N(R^9)-, -N(R^9)C(O)-, -N(R^9)SO$_2$-, and –N(R^9)-C(O)-N(R^{10})-;

c) L=Cy-(CH$_2$)$_k$-W-

wherein,

Cy is C_1-C_{15} alkyl, aminoalkyl, heterocycloalkyl, cycloalkyl, aryl, aryloxy or heteroaryl, each of which may be optionally substituted;

k is 0, 1, 2, 3, 4 or 5;

W is selected from the group consisting of a bond, -O-, -S-, -S(O)-,

-S(O)$_2$-, -N(R^9)-, -C(O)N(R^9)-, -SO$_2$N(R^9)-, -N(R^9)C(O)-, -N(R^9)SO$_2$-, and –N(R^9)-C(O)-N(R^{10})-;

d) L=L^1-W-L^2

L^1 and L^2 are the same or different and independently selected from C_1-C_5 alkyl or C_2-C_5 alkenyl each of which may be optionally substituted which may be optionally substituted;

W is selected from the group consisting of a bond, -O-, -S-, -S(O)-,

-S(O)$_2$-, -N(R^9)-, -C(O)N(R^9)-, -SO$_2$N(R^9)-, -N(R^9)C(O)-, -N(R^9)SO$_2$-, and –N(R^9)-C(O)-N(R^{10})-;

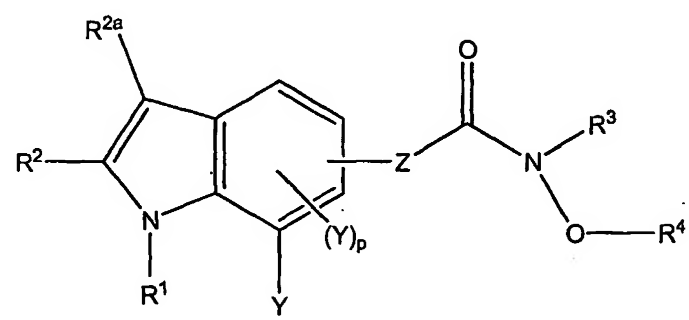
R^9 and R^{10} are the same or different and are independently selected from H, C_1-C_6 alkyl, hydroxyalkyl, heteroalkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl and acyl each of which may be optionally substituted;

Z is a bond or is selected from the group consisting of $-CH_2-$, $-CH_2CH_2-$, $-CH=CH-$ and C_3-C_6 cycloalkyl each of which may be optionally substituted;

or a pharmaceutically acceptable salt or prodrug thereof.

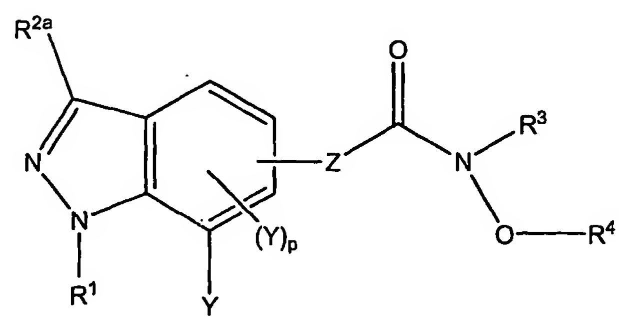
2. A compound according to claim 1 wherein the bond between V and V^1 is a double bond.

3. A compound of claim 1 wherein the compound has the formula (Ib):



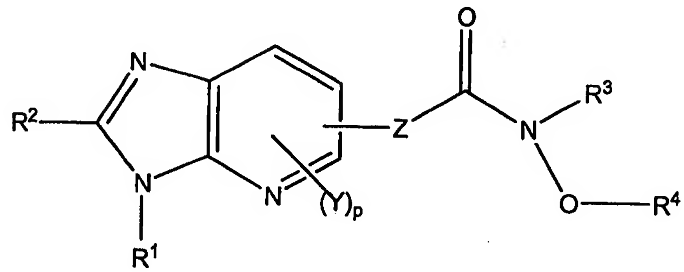
wherein R^1, R^2, R^{2a}, R^3, R^4, Y, p and Z are as defined for compound of formula (I)

4. A compound of claim 1 wherein the compound has the formula (Ic):



wherein R^1, R^{2a}, R^3, R^4, Y, p and Z are as defined for compounds of formula (I).

5. A compound of claim 1 wherein the compound has the formula (Id):



wherein R^1, R^{2a}, R^3, R^4, Y, and Z are as defined for compound of formula (I).

6. A compound according to any one of claims 1 to 5 wherein Z is -CH=CH-.

7. A compound according to any one of claims 1 to 5 wherein Z is attached at ring position 5 or 6.

8. A compound according to any one of claims 1 to 7 where Z is attached at ring position 5.

9. A compound of any one of claims 3 or 4 wherein p = 0.

10. A compound according to claim 4 wherein q = 0.

11. A compound of any one of claims 1 to 10 wherein R^3 = H.

12. A compound according to any one of claims 1 to 11 wherein Y is H.

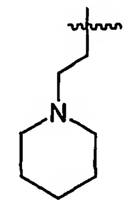
13. A compound according to any one of claims 1 to 12 wherein R^4 = H.

14. A compound according to any one of claims 1 to 13 wherein R^1 is selected from the group consisting of: H, hydroxyalkyl, alkyl, heteroalkyl, alkoxyalkyl, arylalkyl, heteroarylalkyl, aminoalkyl, heterocycloalkylheteroalkyl, heterocycloalkylalkyl and heterocycloalkyl each of which may be optionally substituted as previously stated.

15. A compound according to any one of claims 1 to 14 wherein R^1 is arylalkyl.

16. A compound according to any one of claims 1 to 15 wherein R^1 is benzyl or phenethyl.

17. A compound according to any one of claims 1 to 13 wherein R^1 is selected from the group consisting of:

$HO-(CH_2)_3-$, $Ph-CH_2-$,  .

18. A compound according to any one of claims 1 to 17 wherein R^2 is selected from the group consisting of H, alkyl, hydroxyalkyl, alkoxyalkyl, aryl, heteroaryl, heteroalkyl, cycloalkyl, heterocycloalkylalkyl, heterocycloalkyl heteroalkyl, arylalkyl, heteroarylalkyl, aryl heteroalkyl, heteroarylheteroalkyl, and L, each of which may be optionally substituted as previously stated.

19. A compound according to any one of claims 1 to 18 wherein R^2 = H.

20. A compound according to any one of claims 1 to 18 wherein R^2 is arylalkyl.

21. A compound according to claim 20 wherein R^{20} is phenethyl.

22. A compound according to any one of claims 1 to 21 wherein R^{2a} is selected from the group consisting of H, alkyl, aryl, heteroaryl, heteroalkyl, cycloalkyl, heterocycloalkylalkyl, heterocycloalkylheteroalkyl, arylheteroalkyl, heteroarylheteroalkyl and L, each of which may be optionally substituted as previously stated.

23. A compound according to claim 22 wherein R^{2a} is selected from the group consisting of heterocycloalkylalkyl, heterocycloalkylheteroalkyl, arylheteroalkyl, and heteroarylheteroalkyl each of which may be optionally substituted.

24. A compound according to claim 23 wherein R^{2a} has the formula:

$$Ar-(CH_2)_r-NR^9-(CH_2)_s-$$

wherein Ar is aryl;

r and s are integers independently selected from 0 to 6;

R^9 is selected from the group consisting of H, C_1-C_6 alkyl, hydroxyalkyl, heteroalkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl, and heteroarylalkyl and acyl each of which may be optionally substituted.

25. A compound according to claim 24 wherein r = 2 and s = 1.

26. A compound according to claim 23 wherein R^{2a} has the formula:

$$\text{Het-}(CH_2)_r\text{-}NR^9\text{-}(CH_2)_s\text{—}$$

wherein Het is heterocycloalkyl;

r and s are integers independently selected from 0 to 6;

R^9 is selected from the group consisting of H, C_1-C_6 alkyl, hydroxyalkyl, heteroalkyl, C_4-C_9 cycloalkyl, C_4-C_9 heterocycloalkyl, aryl, heteroaryl, arylalkyl; and heteroarylalkyl and acyl each of which may be optionally substituted.

27. A compound according to claim 26 wherein r = 2 and s = 1.

28. A compound according to any one of claims 1 to 21 wherein R^{2a} is a group of formula:

Cy-L_1-W-

wherein

Cy is C_1-C_{15} alkyl, aminoalkyl, heteroalkyl heterocycloalkyl, cycloalkyl, aryl, aryloxy or heteroaryl, each of which may be optionally substituted;

L^1 is selected from the group consisting of C_1-C_5 alkyl or C_2-C_5 alkenyl each of which may be optionally substituted;

W is selected from the group consisting of a bond, -O-, -S-, -S(O)-,
-$S(O)_2$-, -$N(R^9)$-, -$C(O)N(R^9)$-, -$SO_2N(R^9)$-, -$N(R^9)C(O)$-, -$N(R^9)SO_2$-, and –$N(R^9)$-C(O)-$N(R^{10})$-;

29. A compound according to claim 28 R^{2a} is a group of formula:

$Cy\text{-}L^1\text{-}N(R^9)C(O)\text{-}$

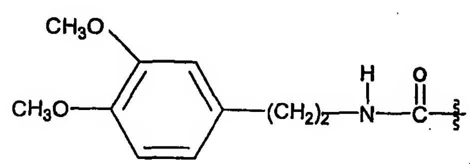
wherein

Cy is C_1-C_{15} alkyl, aminoalkyl, heterocycloalkyl, cycloalkyl, aryl, aryloxy or heteroaryl, each of which may be optionally substituted;.

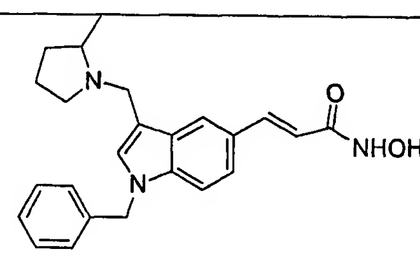
L^1 is selected from the group consisting of C_1-C_5 alkyl, which may be optionally substituted.

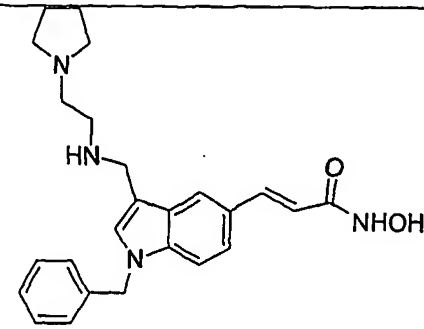
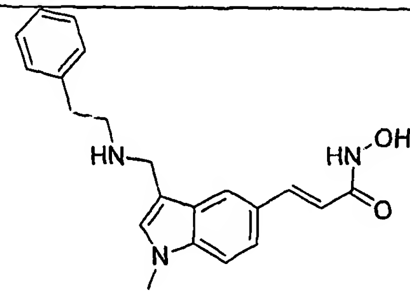
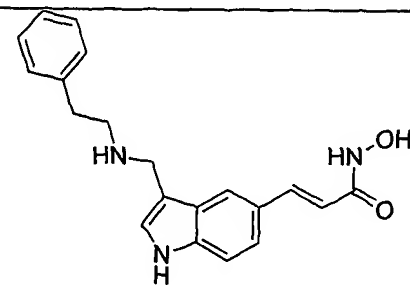
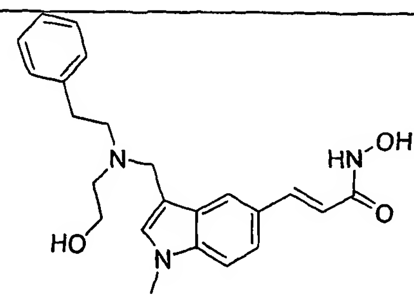
30. A compound according to any one of claims 24 to 29 wherein R^9 is selected from the group consisting of H, alkyl and hydroxyalkyl.

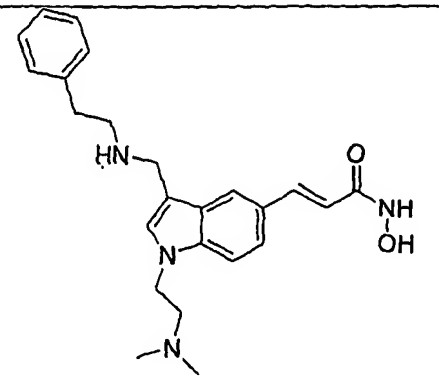
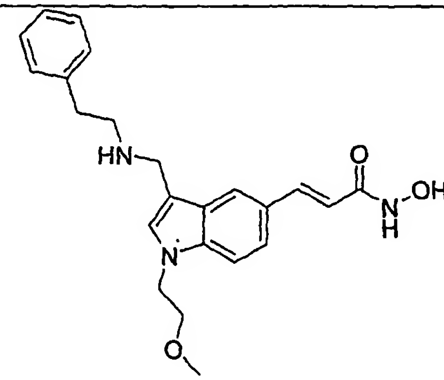
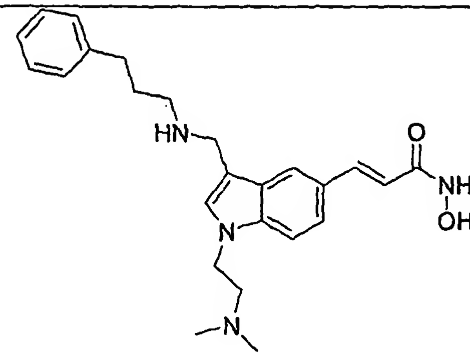
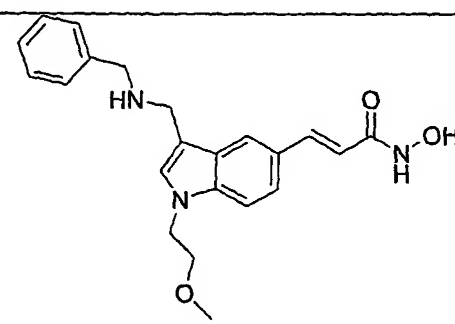
31. A compound according to claim 29 wherein R^{2a} is a group of formula:

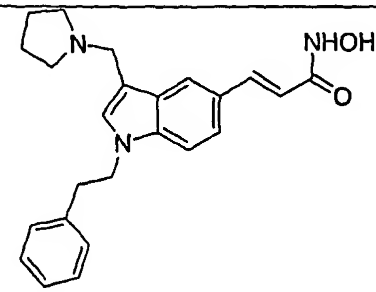
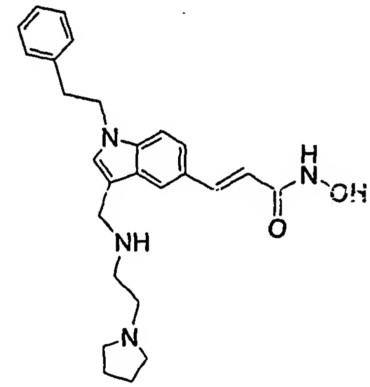
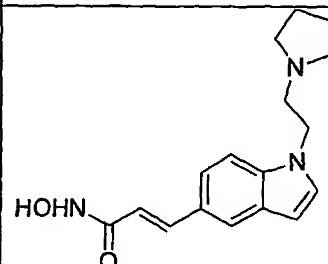
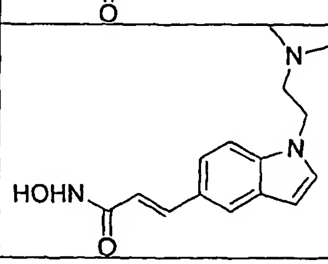
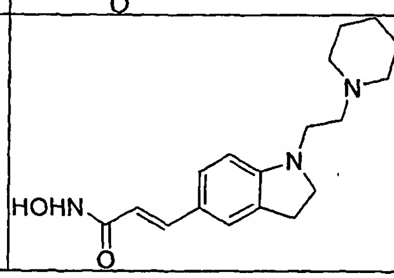


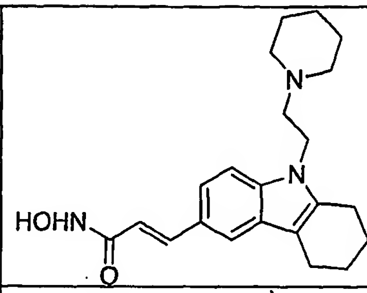
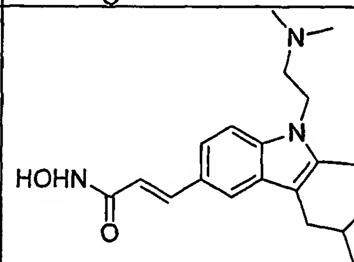
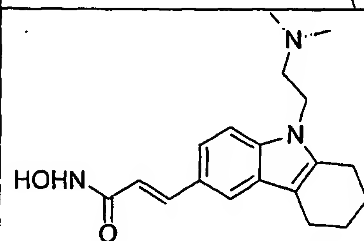
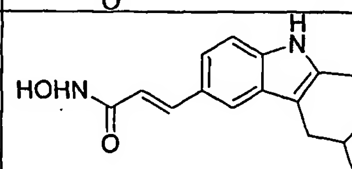
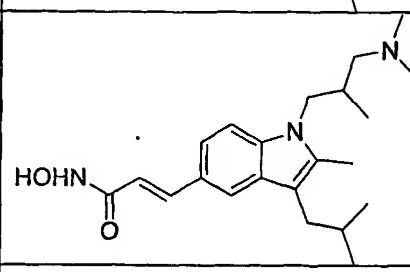
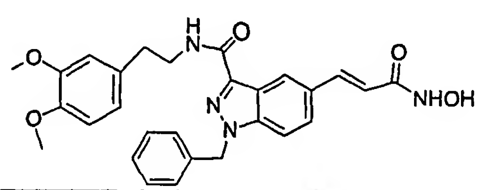
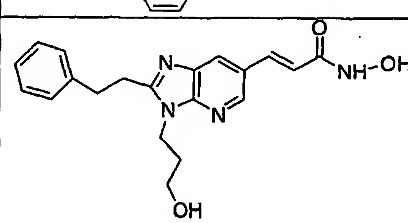
32. The compound of claim 1 wherein the compound is selected from compounds, and their pharmaceutically acceptable salts, selected from the group consisting of

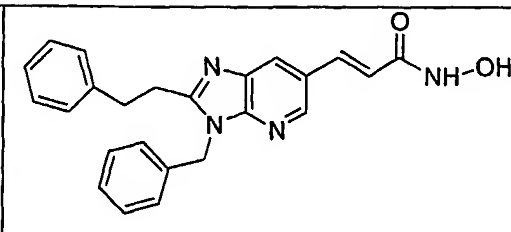
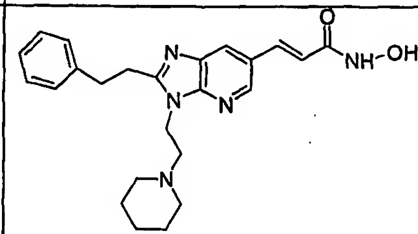
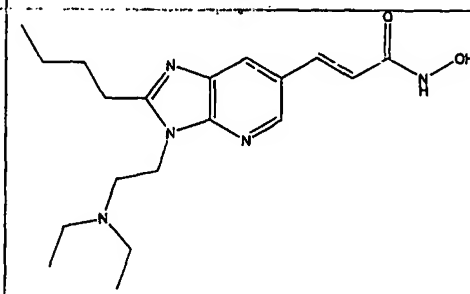
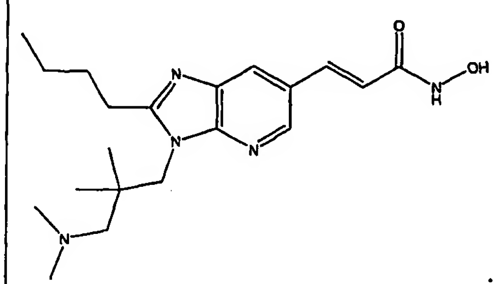
Compound name	Structure
3-[1-Benzyl-3-(2-methyl-pyrrolidin-1-ylmethyl)-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide	

3-{1-Benzyl-3-[(2-pyrrolidin-1-yl-ethylamino)-methyl]-1*H*-indol-5-yl}-*N*-hydroxy-acrylamide	
N-Hydroxy-3-[1-methyl-3-(phenethylamino-methyl)-1*H*-indol-5-yl]-acrylamide	
N-Hydroxy-3-[3-(phenethylamino-methyl)-1*H*-indol-5-yl]-acrylamide	
N-Hydroxy-3-(3-{[(2-hydroxy-ethyl)-phenethyl-amino]-methyl}-1-methyl-1*H*-indol-5-yl)-acrylamide	

3-[1-(2-Dimethylamino-ethyl)-3-(phenethylamino-methyl)-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide	
N-Hydroxy-3-[1-(2-methoxy-ethyl)-3-(phenethylamino-methyl)-1*H*-indol-5-yl]-acrylamide	
3-{1-(2-Dimethylamino-ethyl)-3-[(3-phenyl-propylamino)-methyl]-1*H*-indol-5-yl}-*N*-hydroxy-acrylamide	
3-[3-(Benzylamino-methyl)-1-(2-methoxy-ethyl)-1H-indol-5-yl]-*N*-hydroxy-acrylamide	

N-Hydroxy-3-(1-phenethyl-3-pyrrolidin-1-ylmethyl-1*H*-indol-5-yl)-acrylamide	
N-Hydroxy-3-{1-phenethyl-3-[(2-pyrrolidin-1-yl-ethylamino)-methyl]-1*H*-indol-5-yl}-acrylamide	
N-Hydroxy-3-[1-(2-pyrrolidin-1-yl-ethyl)-1*H*-indol-5-yl]-acrylamide	
3-[1-(2-Dimethylamino-ethyl)-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide	
N-Hydroxy-3-[1-(2-piperidin-1-yl-ethyl)-2,3-dihydro-1*H*-indol-5-yl]-acrylamide	

N-Hydroxy-3-[9-(2-piperidin-1-yl-ethyl)-6,7,8,9-tetrahydro-5*H*-carbazol-3-yl]-acrylamide	
3-[1-(2-Dimethylamino-ethyl)-3-isobutyl-2-methyl-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide	
3-[9-(2-Dimethylamino-ethyl)-6,7,8,9-tetrahydro-5*H*-carbazol-3-yl]-*N*-hydroxy-acrylamide	
N-Hydroxy-3-(3-isobutyl-2-methyl-1*H*-indol-5-yl)-acrylamide	
3-[1-(3-Dimethylamino-2-methyl-propyl)-3-isobutyl-2-methyl-1*H*-indol-5-yl]-*N*-hydroxy-acrylamide	
1-Benzyl-5-(2-hydroxycarbamoyl-vinyl)-1*H*-indazole-3-carboxylic acid [2-(3,4-dimethoxy-phenyl)-ethyl]-amide	
N-Hydroxy-3-[3-(3-hydroxyl-propyl)-2-phenethyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl]-acrylamide	

3-(3-Benzyl-2-phenethyl-3*H*-imidazo[4,5-*b*]pyridin-6-yl)-*N*-hydroxy-acrylamide	
N-hydroxy-3-[2-phenethyl-3-(2-piperidin-1-yl-ethyl)-3*H*-imidazo[4,5-*b*]pyridin-6-yl]-acrylamide	
3-[2-Butyl-3-(2-diethylamino-ethyl)-3H-imidazo[4,5-b]pyridin-6-yl]-*N*-hydroxy-acrylamide	
3-[2-Butyl-3-(3-dimethylamino-2,2-dimethyl-propyl)-3*H*-imidazo[4,5-b]pyridin-6-yl]-*N*-hydroxy-acrylamide	

33. A pharmaceutical composition including a compound according to any one of claims 1 to 32 and a pharmaceutically acceptable diluent, excipient or carrier.

34. Use of a compound according to any one of claims 1 to 32 in the preparation of a medicament for the treatment of a disorder caused by, associated with or accompanied by disruptions of cell proliferation and/or angiogenesis.

35. A use according to claim 34 wherein the disorder is a proliferative disorder.

36. A use according to claim 35 wherein the proliferative disorder is cancer.

37. A method of treatment of a disorder caused by, associated with or accompanied by disruptions of cell proliferation and/or angiogenesis in a patient the method including administration of a therapeutically effective amount of a compound according to any one of claims 1 to 32 to the patient.

38. A method according to claim 37 wherein the disorder is a proliferative disorder.

39. A method according to claim 37 wherein the disorder is cancer.

40. Use of a compound according to any one of claims 1 to 32 or a pharmaceutical composition according to claim 33 to modify deacetylase activity.

41. A use according to claim 40 wherein the deacetylase activity is histone deacetylase activity.

42. A use according to claim 40 wherein the deacetylase activity is class I histone deacetylase activity.

43. A use according to claim 41 or 42 wherein the histone deacetylase is HDAC1.

44. A use according to claim 41 or 42 wherein the histone deacetylase is HDAC8.

45. A method of treatment of a disorder that can be treated by the inhibition of histone deacetylase in a patient including administration of a therapeutically effective amount of a compound according to any one of claims 1 to 32 to the patient.

46. A method according to claim 45 wherein the disorder is selected from the group consisting of Proliferative disorders (e.g. cancer); Neurodegenerative diseases including Huntington's Disease, Polyglutamine diseases, Parkinson's Disease, Alzheimer's Disease, Seizures, Striatonigral degeneration, Progressive supranuclear palsy, Torsion dystonia, Spasmodic torticollis and dyskinesia, Familial tremor, Gilles de la Tourette syndrome, Diffuse Lewy body disease, Pick's disease, Intracerebral haemorrhage Primary lateral sclerosis, Spinal muscular atrophy, Amyotrophic lateral sclerosis, Hypertrophic interstitial polyneuropathy, Retinitis pigmentosa, Hereditary optic atrophy, Hereditary spastic paraplegia, Progressive ataxia and Shy-Drager syndrome; Metabolic diseases including Type 2 diabetes; Degenerative Diseases of the Eye including Glaucoma, Age-related macular degeneration, macular myopic

degeneration, Rubeotic glaucoma, Interstitial keratitis, Diabetic retinopathy, Peter's anomaly, retinal degeneration, Cellophane Retinopathy; Cogan's Dystrophy; Corneal Dystrophy; Iris Neovascularization (Rubeosis); Neovascularization of the Cornea; Retinopathy of Prematurity; Macular Edema; Macular Hole; Macular Pucker; Marginal Blepharitis, Myopia, nonmalignant growth of the conjunctiva; Inflammatory diseases and/or Immune system disorders including Rheumatoid Arthritis (RA), Osteoarthritis, Juvenile chronic arthritis, Graft versus Host disease, Psoriasis, Asthma, Spondyloarthropathy, Crohn's Disease, inflammatory bowel disease, Colitis Ulcerosa, Alcoholic hepatitis, Diabetes, Sjoegrens's syndrome, Multiple Sclerosis, Ankylosing spondylitis, Membranous glomerulopathy, Discogenic pain, Systemic Lupus Erythematosus, allergic contact dermatitis; Disease involving angiogenesis including cancer, psoriasis, rheumatoid arthritis; Psychological disorders including bipolar disease, schizophrenia, depression and dementia; Cardiovascular Diseases including Heart failure, restenosis, cardiac hypertrophy and arteriosclerosis; Fibrotic diseases including liver fibrosis, lung fibrosis, cystic fibrosis and angiofibroma; Infectious diseases including Fungal infections, such as Candida Albicans, Bacterial infections, Viral infections, such as Herpes Simplex, Protozoal infections, such as Malaria, Leishmania infection, Trypanosoma brucei infection, Toxoplasmosis and coccidiosis and Haematopoietic disorders including thalassemia, anemia and sickle cell anemia.

47. Use of a compound according to any one of claims 1 to 32 in the preparation of a medicament for the treatment of a disorder that can be treated by the inhibition of histone deacetylase.

48. A use according to claim 47 wherein the disorder is selected from the group consisting of Proliferative disorders (e.g. cancer); Neurodegenerative diseases including Huntington's Disease, Polyglutamine diseases, Parkinson's Disease, Alzheimer's Disease, Seizures, Striatonigral degeneration, Progressive supranuclear palsy, Torsion dystonia, Spasmodic torticollis and dyskinesis, Familial tremor, Gilles de la Tourette syndrome, Diffuse Lewy body disease, Pick's disease, Intracerebral haemorrhage Primary lateral sclerosis, Spinal muscular atrophy, Amyotrophic lateral sclerosis, Hypertrophic interstitial polyneuropathy, Retinitis pigmentosa, Hereditary optic atrophy, Hereditary spastic paraplegia, Progressive ataxia and Shy-Drager syndrome; Metabolic diseases including Type 2 diabetes; Degenerative Diseases of the Eye including Glaucoma, Age-related macular degeneration, macular myopic degeneration, Rubeotic glaucoma, Interstitial keratitis, Diabetic retinopathy, Peter's anomaly, retinal degeneration, Cellophane Retinopathy; Cogan's Dystrophy; Corneal

Dystrophy; Iris Neovascularization (Rubeosis); Neovascularization of the Cornea; Retinopathy of Prematurity; Macular Edema; Macular Hole; Macular Pucker; Marginal Blepharitis, Myopia, nonmalignant growth of the conjunctiva; Inflammatory diseases and/or Immune system disorders including Rheumatoid Arthritis (RA), Osteoarthritis, Juvenile chronic arthritis, Graft versus Host disease, Psoriasis, Asthma, Spondyloarthropathy, Crohn's Disease, inflammatory bowel disease, Colitis Ulcerosa, Alcoholic hepatitis, Diabetes, Sjoegrens's syndrome, Multiple Sclerosis, Ankylosing spondylitis, Membranous glomerulopathy, Discogenic pain, Systemic Lupus Erythematosus, allergic contact dermatitis; Disease involving angiogenesis including cancer, psoriasis, rheumatoid arthritis; Psychological disorders including bipolar disease, schizophrenia, depression and dementia; Cardiovascular Diseases including Heart failure, restenosis, cardiac hypertrophy and arteriosclerosis; Fibrotic diseases including liver fibrosis, lung fibrosis, cystic fibrosis and angiofibroma; Infectious diseases including Fungal infections, such as Candida Albicans, Bacterial infections, Viral infections, such as Herpes Simplex, Protozoal infections, such as Malaria, Leishmania infection, Trypanosoma brucei infection, Toxoplasmosis and coccidiosis and Haematopoietic disorders including thalassemia, anemia and sickle cell anemia.

49. A method for inhibiting cell proliferation including administration of an effective amount of a compound according to any one of claims 1 to 32.

50. Use of a compound according to any one of claims 1 to 32 in the preparation of a medicament for inhibiting cell proliferation.

51. A method of treatment of a neurodegenerative disorder in a patient including administration of a therapeutically effective amount of a compound according to any one of claims 1 to 32 to the patient.

52. A method according to claim 48 wherein the neurodegenerative disorder is Huntington's Disease.

53. Use of a compound according to any one of claims 1 to 32 in the preparation of a medicament for the treatment of a neurodegenerative disorder.

54. A use according to claim 53 wherein the neurodegenerative disorder is Huntington's Disease.

55. A method of treatment of an inflammatory disease and/or immune system disorder in a patient including administration of a therapeutically effective amount of a compound according to any one of claims 1 to 32 to the patient.

56. A method according to claim 55 wherein the inflammatory disease and/or immune system disorder is rheumatoid arthritis.

57. A method according to claim 55 wherein the inflammatory disease and/or immune system disorder is systemic lupus erythematosus.

58. Use of a compound according to any one of claims 1 to 32 in the preparation of a medicament for the treatment of an inflammatory disease and/or immune system disorder.

59. A use according to claim 58 wherein the inflammatory disease and/or immune system disorder is rheumatoid arthritis.

60. A use according to claim 58 wherein the inflammatory disease and/or immune system disorder is systemic lupus erythematosus.

61. The use of a compound according to any one of claims 1 to 32 in the manufacture of a medicament for the treatment of cancer.

62. A use according to claim 61 wherein the cancer is a hematologic malignancy.

63. A use according to claim 62 wherein the hematologic malignancies are selected from a group consisting of B-cell lymphoma, T-cell lymphoma and leukemia.

64. A use according to claim 61 wherein the cancer is a solid tumor.

65. A use according to claim 64 wherein the solid tumor is selected from the group consisting of breast cancer, lung cancer, ovarian cancer, prostate cancer, head and neck cancer, renal cancer, gastric cancer, colon cancer, pancreatic cancer and brain cancer.

66. A method of treatment of a proliferative disorder in patient including administration of a therapeutically effective amount of a compound according to any one of claims 1 to 32 to the patient.

67. Use of a compound according to any one of claims 1 to 32 in the preparation of a medicament for the treatment of a proliferative disorder.

68. A method of treatment of cancer in patient including administration of a therapeutically effective amount of a compound according to any one of claims 1 to 32 to the patient.

69. A method according to claim 68 wherein the cancer is a hematologic malignancy.

70. A method according to claim 69 wherein the hematologic malignancy is selected from the group consisting of B-cell lymphoma, T-cell lymphoma and leukemia.

71. A method according to claim 68 wherein the cancer is a solid tumor.

72. A method according to claim 71 wherein the solid tumor is selected from the group consisting of breast cancer, lung cancer, ovarian cancer, prostate cancer, head and neck cancer, renal cancer, gastric cancer, colon cancer, pancreatic cancer and brain cancer.

73. Use of a compound according to any one of claims 1 to 32 in the manufacture of a medicament for the induction of apoptosis of tumor cells.

74. A method of induction of apoptosis of a cell including contacting the cell with an effective amount of a compound according to any one of claims 1 to 32.

75. A method of treatment of a degenerative eye disease in a patient including administration of a therapeutically effective amount of a compound according to any one of claims 1 to 32 to the patient.

76. A method according to claim 75 wherein the degenerative eye disease is selected from the group consisting of macular degeneration, retinal degeneration and glaucoma.

77. Use of a compound according to any one of claims 1 to 32 in the preparation of a medicament for the treatment of a degenerative eye disease.

78. A use according to claim 77 wherein the degenerative eye disease is selected from the group consisting of macular degeneration, retinal degeneration and glaucoma.

INTERNATIONAL SEARCH REPORT

International application No. PCT/SG2006/000065

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.

C07D 403/06 (2006.01)	*A61P 27/02* (2006.01)	*C07D 231/56* (2006.01)	*A61K 31/404* (2006.01)
A61P 35/00 (2006.01)	*C07D 403/12* (2006.01)	*A61K 31/4188* (2006.01)	*C07D 209/14* (2006.01)
C07D 471/04 (2006.01)	*A61P 3/10* (2006.01)	*C07D 209/18* (2006.01)	*A61P 25/28* (2006.01).
C07D 209/20 (2006.01)			

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
STN: CAS OnLine: Substructure search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Witty DR. et al. Tetrahedron Letters, Vol. 37, pp. 3067-3070, 1996. "Synthesis of Conformationally Restricted Analogues of the Tryptophanyl tRNA Synthetase Inhibitor Indolmycin" see in particular compound 8 on page 3068.	1-3,7 9,12,14,18,19, 22
X	Gupta S.P. et al. Letters in Drug Design & Discovery, 2005,vol 2, Pages 522-528. 'Quantitative Structure –Activity Relationship Studies on Matrix Metalloproteinase Inhibitors: Bicyclic Heteroaryl Hydroxamic Acid Analogs" See table 2	1,2,7,11,13, 14,22
X	Bare T.M. et al. Journal of Medicinal Chemistry 1989, vol 32, pages 2561-2573 "Synthesis and Structure –Activity Relationships of a Series of Anxioselective Pyrazolopyridine Ester and Amide Anxiolytic Agents" See compound 30 table 1	1,2,7,11,14,22

[X] Further documents are listed in the continuation of Box C   [X] See patent family annex

* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search 25 May 2006	Date of mailing of the international search report 7 JUN 2006
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2002/010137 A2 (SIGNAL PHARMACEUTICALS INC.) 7 February 2002 See in particular examples 104 and 106	1,2,4,7-14,19, 22, 33-36,47-74

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SG2006/000065

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	2002/010137	AU	79089/01	AU	2004232981	BR	I0409417
		CA	2417650	CA	2522682	EP	1313711
		EP	1618093	NZ	524045	US	6897231
		US	2002103229	US	2004077877	US	2004127536
		US	2005009876	US	2005107457	WO	2004/094388
		ZA	200300886				

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.

END OF ANNEX